ABSTRACTS

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American College of Clinical Pharmacy
2001 Annual Meeting
October 21–24 • 2001
Tampa Marriott Waterside
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Encore Presentations: Abstracts marked with an "E" are Encore Presentations. Encore Presentations undergo the same peer review process as do Original Presentations, but may have been presented elsewhere or published in abstract form only prior to the 2001 Annual Meeting. For Encore Presentations, the abstract title, authors, and original citation (if provided) are published in *Pharmacotherapy*. The full abstract will be published in the meeting program book.

ORIGINAL RESEARCH

These papers describe original research in therapeutics, pharmacokinetics, pharmacodynamics, pharmacoeconomics, pharmacoepidemiology, and pharmacogenomics.

Adverse Drug Reactions/Drug Interactions

1. Effects of the cyclooxygenase-2 specific inhibitor celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibition. *William B. White, M.D.,* Andrew Whelton, M.D., Jeffrey Kent, M.D., James Lefkowith, M.D., Ken Verburg, M.D.; University of Connecticut Health Center, Farmington, CT; Johns Hopkins, Baltimore, MD; Pharmacia Clinical Research, Skokie, IL.

BACKGROUND: Nonselective nonsteroidal anti-inflammatory agents (NSAIDs) may interfere with the efficacy of ACE inhibitors with increases in mean arterial pressure. Less is known about celecoxib, the new cyclooxygenase-2 (COX-2) specific inhibitor. Therefore, we studied the effects of celecoxib versus placebo on 24-hour BP in ACE inhibitor-treated hypertensives.
METHODS: In this randomized, double-blind, placebo-controlled, parallel group study, hypertensive patients were treated and controlled (clinic diastolic BP < 90 mm Hg) with lisinopril (10 to 40 mg QD) and 24-hour baseline BPs were obtained. Patients were randomized to receive either celecoxib, 400 mg TDD (n=91) or placebo (n=87) for 4 weeks and 24 hour BP were repeated.
RESULTS: Baseline demographics and BPs were similar for the 2 groups. Changes from baseline in the 24 hour, daytime and nighttime BP were:

BP (mm Hg)	Δ from Baseline in ACE-inhibitor patients (mean ± SE)			
	Celecoxib	Placebo	Difference	p value
24-hour Systolic BP	2.62 ± 0.86	1.0 ± 0.98	1.58	0.195
24-hour Diastolic BP	1.48 ± 0.62	0.26 ± 0.64	1.22	0.126
Daytime Systolic BP	2.97 ± 0.92	1.01 ± 1.03	1.96	0.139
Daytime Diastolic BP	1.67 ± 0.68	0.41 ± 0.68	1.26	0.133
Nighttime Systolic BP	1.37 ± 1.03	1.10 ± 1.20	0.27	0.801
Nighttime Diastolic BP	0.62 ± 0.78	-0.28 ± 1.0	0.90	0.433

CONCLUSIONS: Celecoxib had no significant effect on the 24-hour antihypertensive effect of lisinopril. The changes observed in 24-hour BP (1.58/1.22 mm Hg) are clinically insignificant and are less than what has been reported for nonselective NSAIDs in ACE inhibitor treated patients.

2. The pharmacokinetics of vardenafil, a new selective PDE5 inhibitor, are not affected by the antacid, Maalox 70™. *Gabrielle Rohde, M.D.,* Georg Wensing, M.D., R. Sachse, M.D.; Bayer AG, Elberfeld, Germany; Bayer AG, Cologne, Germany.

PURPOSE: Vardenafil is currently undergoing phase III trials for the oral treatment of erectile dysfunction. Phase II studies have indicated that vardenafil improves erectile function and is well tolerated at doses up to 20 mg. Because some drugs have shown a retardation of absorption when taken with antacids, vardenafil absorption with or without a commonly used antacid, Maalox 70™, was investigated in a non-blinded 2-way crossover study.
METHODS: Twelve healthy men, ages 23 to 44, were randomized to take one 20 mg vardenafil tablet with or without Maalox (10 ml, 400 mg magnesium hydroxide and 900 mg aluminum oxide). For evaluation of standard pharmacokinetic parameters, multiple blood samples were taken over 24 hours and plasma concentrations of vardenafil were determined.
RESULTS: The mean bioavailability of vardenafil was unchanged when taken with the antacid (97 % of the bioavailability of vardenafil alone). The median t_{max} occurred at 0.75 and 0.77 hours without or with the antacid, respectively. The $t_{1/2}$ were similar (5.8 and 5.5 hours). C_{max} was slightly higher in the vardenafil alone group (19.1 µg/L versus 15.7 µg/L), resulting in a C_{max} ratio (vardenafil with the antacid/vardenafil alone) of 82%. Vardenafil was well tolerated in both treatment arms with mild headache being the only treatment–related adverse event.
CONCLUSION: This study showed that vardenafil absorption and clearance was not affected by the coadministration of an antacid such as Maalox.

3. The pharmacokinetics of vardenafil, a new selective PDE5 inhibitor, is minimally affected by coadministration with cimetidine or ranitidine. *Gabrielle Rohde, M.D.,* Georg Wensing, M.D., Singrun Unger, Ph.D., R. Sachse, M.D.; Bayer AG, Elberfeld, Germany; Bayer AG, Cologne, Germany.

PURPOSE: Vardenafil is currently being evaluated in phase III trials as a treatment for impaired erectile function. The influence of changing stomach pH and of non-specific P450 enzyme inhibition on the absorption and bioavailability of vardenafil was investigated in 12 healthy males, ages 24-44, in a randomized, open, three-way crossover study.
METHODS: After 3 days of oral pretreatment with either 400 mg cimetidine BID (which modifies stomach pH and inhibits cytochrome P450 enzymes) or 150 mg ranitidine BID (which modifies only the stomach pH), men were given a 20 mg tablet of vardenafil on the fourth day together with cimetidine or ranitidine. In an additional treatment arm, 20 mg vardenafil was given alone. Blood samples were taken at frequent intervals and safety was routinely monitored.
RESULTS: Bioavailability of vardenafil with cimetidine was slightly increased (by 12 %) whereas with ranitidine it was unchanged suggesting that cimetidine's effect on vardenafil's bioavailability was the result of P450 enzyme inhibition (table). $t_{1/2}$ and t_{max} were unchanged. The most common AEs were mild headache and rhinitis.
Table: Vardenafil pharmacokinetic parameters

Parameter	Vardenafil alone	Vardenafil + Cimetidine	Vardenafil + Ranitidine
C_{max} (µg•h/L)§	18.7 ± 1.7	19 ± 1.6	20.7 ± 1.9
AUC (µg•h/L)§	56.8 ± 1.6	64.9 ± 1.6	58.9 ± 1.9
t_{max} (h)†	0.88 (0.50-1.50)	0.75 (0.75-2.00)	0.75 (0.50-2.00)
$t_{1/2}$ (h)§	3.9 ± 1.3	4.2 ± 1.3	4.0 ± 1.3

§geometric mean ±standard deviation; †median (range)

CONCLUSION: These findings have positive implications for patients, with impaired erectile function, who use these drugs for treatment of stomach acidity.

4. Vardenafil, a new selective PDE5 inhibitor, produces no interaction with digoxin. *Gabrielle Rohde, M.D.,* Richard-Josef Bauer, M.D., Singrun Unger, Ph.D., Gertrud Ahr, Ph.D., Georg Wensing, M.D., Jochen Kuhlmann, M.D.; Bayer AG, Elberfeld, Germany.

PURPOSE: Vardenafil, a potential new treatment for impaired erectile function, is currently being evaluated in phase III trials. Vardenafil's influence on the pharmacokinetics of digoxin was investigated in a randomized, double-blind, placebo-controlled, two-fold crossover study.
METHODS: Nineteen healthy male subjects, ages 23-43, were given a 20 mg oral dose of vardenafil or a placebo every other day over 14 days concomitantly with a daily 0.375 mg oral dose of digoxin and then crossed-over to the other treatment arm. Blood samples were taken at frequent intervals and routine safety monitoring was performed.
RESULTS: At steady state, on the 14th day of each study period, the primary pharmacokinetic parameters of digoxin AUC and $C_{trough,}$ (as representative parameter for minimum effective concentrations) were not affected by the presence of vardenafil.

	Digoxin + 20 mg Vardenafil† (n=19)	Digoxin + Placebo† (n=19)	Ratio of treatments * 100 % (vardenafil + digoxin / placebo + digoxin)
$AUC_{TAU,ss}$	17.9±1.3 (µg*h/L)	16.5±1.3 (µg*h/L)	108.2 %, (103.2 % - 113.4 %)††
$C_{trough,ss}$	0.64±1.3 (µg/L)	0.61±1.3 (µg/L)	103.5 %, (99.6 % - 107.5 %)††

†values are geometric mean/ SD; †† point estimate, (90 % CI)

Both values were within the 90 % confidence interval of (80-125%) demonstrating a lack of interaction. The most common adverse event was mild to moderate headache. A total of 13/19 patients in the vardenafil group reported adverse events compared to 7/19 in the placebo group.
CONCLUSION: These results indicate that the plasma levels of digoxin in men were not altered when they also took vardenafil.

5. The prevalence of patients at-risk for anti-inflammatory-induced renal toxicity and blood pressure destabilization: data from managed care. *Carolyn Harley, Ph.D.,* Samuel Wagner, Ph.D., Thomas Burke, Pharm.D.,

Michael Nelson, Pharm.D.; Ingenix Pharmaceutical Services, Eden Prairie, MN; Pharmacia Corporation, Peapack, NJ.

BACKGROUND: It is well known that NSAIDs are associated with prostaglandin -mediated renal side effects. Since prostaglandins promote diuresis and vasodilation, the prostaglandin inhibition of NSAIDs is also associated with blood pressure (BP) increases.
PURPOSE: To determine the prevalence of COX-2 inhibitor and NSAID users at risk of adverse renal events and BP destabilization in managed care.
METHODS: A retrospective, longitudinal claims data analysis in a large national IPA health plan identified members with a rheumatoid arthritis (RA) or osteoarthritis (OA) diagnosis and with an incident claim for celecoxib, rofecoxib or other non-COX-specific NSAID from 10/1/99 to 9/30/2000. Multivariate logistic regression models were used to determine whether baseline risk factors were related to choice of therapy.
RESULTS: The prevalence of risk factors was high (~50%), and are listed below. In the multivariate models, COX-2 users were older and had significantly more risk factors than NSAID users. Celecoxib users were 45% more likely to have RA (OR=1.45; 1.30-1.63; p<0.001).

Clinical History	Celecoxib (n=6,779)	Rofecoxib (n=7,189)	Other NSAID (n=63,584)	All Subjects (n=77,552)
CHF (%)	8.98	9.08	4.55	5.36
Hypertension (%)	43.94	42.68	30.03	32.42
Acute renal failure (%)	0.62	0.47	0.14	0.21
Nephritis (%)	2.14	2.00	1.04	1.23
Fluid or electrolyte imbalance (%)	6.42	6.30	3.98	4.41
Edema (%)	11.14	11.23	7.69	8.32

CONCLUSIONS: Subjects with renal/HTN risk factors are more likely to receive a COX-2 compared to an NSAID. Clinicians treating OA/RA patients with risk factors for renal adverse effects should not ignore the potential effects of arthritis medications on renal function and BP control.

6. Coadministration of rosuvastatin does not alter the pharmacokinetics of digoxin. John V. Kemp, HNC, *Paul D. Martin, M.Phil.,* Olise, M.D., Nwose MRCPath, Aaron L. Dane, M.Sc., Dennis W. Schneck, M.D.; AstraZeneca, Alderley Park, Cheshire, United Kingdom; AstraZeneca, Wilmington, DE.

PURPOSE: To assess the effect of rosuvastatin on the pharmacokinetics of a single dose of digoxin.
METHODS: This was a double-blind, randomized, 2-way crossover, single-center study (4522IL/0013). During period A, eighteen healthy subjects were randomized to receive either 12 daily oral doses of rosuvastatin 40 mg (Crestor, AstraZeneca) or placebo. A single dose of 0.5 mg digoxin was administered on day 8. In period B subjects received the alternate rosuvastatin or placebo treatment with the 0.5 mg digoxin dose given again on day 8. The number of subjects was sufficient to ensure a 90% chance that the ratio of digoxin geometric lsmeans for AUC and C_{max} (digoxin + rosuvastatin /digoxin + placebo) was contained within the interval 0.74 - 1.35) at the 5% significance level. Plasma and urine samples were obtained at intervals following the digoxin dose and analyzed.
RESULTS: The ratios of glsmeans for AUC and Cmax (digoxin + rosuvastatin /digoxin + placebo) were 1.04 and were contained within the pre-specified limits confirming that rosuvastatin did not produce a clinically significant change in the pharmacokinetics of digoxin. Renal clearance of digoxin was 5% higher when co-administered rosuvastatin.

Parameter	Digoxin (+ Rosuvastatin)	Digoxin (+ Placebo)	Ratio of glsmeans	90% CI for ratio
$AUC_{0\text{-}t}$ (ng.h/ml)	8.14	7.80	1.04	0.88 to 1.24
C_{max} (ng/ml)	2.22	2.12	1.04	0.89 to 1.22

No safety concerns arose from the concomitant administration of the two drugs.
CONCLUSIONS: Coadministration of rosuvastatin did not produce a clinically significant change in the pharmacokinetics of digoxin.

7. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: a systematic review of published case reports. *Patrick J. Medina, Pharm.D., BCOP,* James M. Sipols, Pharm.D. candidate, Sara K. Vesely, Ph.D., James N. George, M.D.; University of Oklahoma Health Science Center, Oklahoma City, OK.

PURPOSE: The frequency of drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) is thought to be low and the number of drugs associated with the etiology TTP-HUS is thought to be few. This study will document the number of drugs associated with TTP-HUS and determine the strength of clinical evidence for individual drugs.
METHODS: The MEDLINE database was searched for literature published between 1966 and May 2001. Articles were retrieved using the MeSH terms “thrombotic thrombocytopenic purpura” and “hemolytic uremic syndrome”. Key words “drug-induced” and “drug-associated” were combined with MeSH headings. The search was supplemented by cross-checking against the bibliographies of retrieved articles for additional reports. *A priori* evaluation rules were established to define levels of evidence for designating drugs as definite, probable, possible, or unlikely causes of TTP-HUS. Each case report will be evaluated independently by two investigators; a third investigator will adjudicate disagreements.
RESULTS: The literature search retrieved 146 articles reporting on 49 different drugs. A preliminary review of the literature has documented two distinct mechanisms of drug-associated TTP-HUS: dose-related toxicity and immune-mediated toxicity. The levels of evidence for each drug as a cause of TTP-HUS will be determined and presented.
CONCLUSION: Drug-associated TTP-HUS may not be rare. Many drugs have been reported as possible causes of TTP-HUS. The strength of evidence supporting this association is important to understand the role of drugs in the etiology of TTP-HUS.

8. Prevalence of drug-drug interactions with carbamazepine and gabapentin: a retrospective claims database analysis. *Amishi B. Shah, Pharm.D.,* Roger Luo, Ph.D.; Wilkes University, Wilkes-Barre, PA; Smith Hanley Consulting, Whippany, NJ.

PURPOSE: The potential for drug interactions with some antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, and valproic acid is well documented, while it is low for gabapentin. However, the lack of documentation of clinical outcomes attributable to drug-interactions in claims databases is a key barrier to conducting retrospective population-based studies. We aimed to describe the prevalence of concomitance of potentially interacting drugs with carbamazepine or gabapentin in an epileptic population using a retrospective claims database.
METHODS: Data were extracted from MarketScan, a proprietary claims database including continuously enrolled patients who receive medical and pharmacy benefits from managed care organizations. We identified continuously enrolled members with ≥1 pharmacy claim for a target AED (carbamazepine or gabapentin) and ≥1 medical claim with an ICD-9-CM code of 345.xx for seizure disorder. We identified drugs with the potential to interact with carbamazepine or gabapentin through a literature search. Following a 45-day drug-free lead-in period, we identified concomitance of target AEDs and potentially interacting drugs in eight 45-day periods (1/1/98 to 12/26/98). A person-period was defined as a period when patients had a supply of carbamazepine or gabapentin on hand. After data transformation, 9,877 and 3,067 person-periods were available for the carbamazepine and gabapentin populations, respectively.
RESULTS: Concomitance of potentially interacting drugs in the carbamazepine and gabapentin groups occurred in 728 (7.4%) and 1 (0.3%) person-periods, respectively.
CONCLUSIONS: This study supplements existing literature by providing a quantitative measure, at the person-period level, of the prevalence of potential drug-drug interactions with carbamazepine and with gabapentin.

9. Co-administration of kaolin with metronidazole or oxytetracycline and oral rehydration salts (ORS) in the treatment of acute diarrhea (drug interaction). *Jude C. Obiakor, B.Pharm.,* Vincent C. Okore, B.Pharm., Simon Abbey, B.Pharm.; Martz Pharmaceuticals LTD, Lagos, Nigeria; University of Nigeria, Nsukka, Nigeria.

PURPOSE: This in vitro study was done in order to (1) rationalize the co-administration of metronidazole or oxytetracycline with Kaolin (adsorbent) or O.R.S but most times with both in the treatment of acute diarrhea, (2) determine the extent to which Kaolin will interfere with the bioavailability of either drug and the effect of O.R.S (electrolyte).
METHOD: Adsorption isotherms were determined for metronidazole and oxytetracycline using aliquots volumes 1 mg %, 2 mg%, 3 mg%, 4 mg%, 5 mg% and 10 mg %, 20 mg%, 30 mg%, 40 mg%, 50 mg%, respectively, of the stock solutions and 1 g of Kaolin. 50 ml solutions of the varied strengths were agitated at equilibrium adsorption (3 h). Filtrates were assayed using spectrophotometric analysis, to determine the amount of drug adsorbed Effects of pH at pH 2-20, pH 6-20, pH 9-20 and NaCl, sucrose, dextrose at concentrations 0.1 N, 0.5 N, 1.0 N; were equally evaluated.
RESULTS: It was deduced that: 1) metronidazole and oxytetracycline were significantly adsorbed by Kaolin in simple aqueous solution; 2) amount of both drugs adsorbed decreased with increase in pH of the solutions; 3) amount of drugs adsorbed decreased with increasing NaCl concentrations; 4) dextrose at all concentrations, increased the adsorption of either drug by Kaolin; 5) dextrose (1.0 N) decreased oxytetracycline adsorption; and 6) increasing the concentration of sucrose solution caused a corresponding increase in amount of metronidazole adsorbed but reduced the adsorption of oxytetracycline.
CONCLUSION: It seems reasonable to conclude that the adsorption interaction between medicinally active metronidazole or oxytetracycline and kaolin occurred to a significant extent in all the cases studied. This interaction could result to decreased bioavailability of either drug and ultimately to therapeutic incompatibility or failure.

10. Association of histamine$_2$ receptor antagonists with thrombocytopenia: incidence and clinical outcome. *Juliana Chan, Pharm.D.,* John Garofalo, Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Histamine$_2$-receptor antagonists (H_2RAs) are widely used in acid-related disorders. H_2RAs have a relatively safe adverse effect profile, however are commonly discontinued if thrombocytopenia develops. The actual

incidence of H_2RA-induced thrombocytopenia is unknown. This retrospective study is to determine the incidence, severity and clinical outcomes in patients with suspected H_2RA-induced thrombocytopenia.
METHODS: Data from patients hospitalized for at least 7 days and receiving at least 1 dose of an H_2RA were collected. Published criteria were used to assess thrombocytopenia and determine whether the actual decrease in platelet count was associated with H_2RA therapy. Patients were considered to have thrombocytopenia if actual platelet counts decreased to ≤ 50% of baseline or to <150,000/uL.
RESULTS: All 250 patients were prescribed ranitidine. Primary indication for ranitidine was for stress ulcer prophylaxis. Surgical patients represented 62% of the study population. Thrombocytopenia occurred in 73 patients (29.2%). The likelihood of ranitidine-induced thrombocytopenia was 6% probable, 19% possible, 60% unlikely and 15% unknown. Ranitidine was discontinued in 29 patients (40%) who developed thrombocytopenia. Platelet counts recovered in 69% of the patients who had therapy discontinued as compared to a 73% recovery rate in patients who continued on ranitidine after developing thrombocytopenia (p=0.123). The number of days until resolution of thrombocytopenia was similar between these two groups (4.2 ± 2.7 days if ranitidine was discontinued versus 4.5 ± 2.6 days if ranitidine was continued). No deaths or bleeding episodes could be attributed to ranitidine-induced thrombocytopenia.
CONCLUSION: The true incidence of H_2RA induced thrombocytopenia does not justify the discontinuation rate of therapy. Patients may not receive needed therapy or may be switched to less effective or more expensive therapy based on inaccurate perceptions of the incidence and severity of this adverse event associated with H_2RAs.

Cardiology

12. Decreased cardiac-related hospitalizations and mortality by target-dose achievement with carvedilol. *David A. Young, Pharm.D.,* Michael K. McGuire, Pharm.D., BCPS, John A. Williamson, Pharm.D., BCPS; Albert Einstein Healthcare Network; Pfizer Inc., Philadelphia, PA.

PURPOSE: A retrospective analysis of members of a managed-care organization with congestive heart failure (CHF) receiving carvedilol was conducted to determine the risk of cardiac-related hospitalization and all-cause mortality in target-dose versus non-target dose groups.
METHODS: Prestige Health is a 50,000 member managed care organization in Philadelphia, Pennsylvania. Pharmacy claims data was used to determine the number of CHF patients who received carvedilol from July 1997 to December 1999. Carvedilol dosing is initiated with 3.125 mg twice daily. The dose is doubled every two weeks until reaching a target dose of 25 mg twice daily. Patients who received at least 10 weeks of carvedilol were chosen to allow adequate time for titration. Seventy-seven members met criteria. The percentage of patients who achieved a target dose during the evaluation period was determined. Rates of cardiac-related hospitalizations and all-cause mortality were determined for the target versus non-target dosing groups.
RESULTS: Twenty-five (23%) of the 77 subjects achieved the target dose. Hospitalization due to cardiac causes (28 versus 5) and deaths (4 versus 0) occurred more often in the non-target group than in the target group, in a dose-related fashion. The rate of hospitalization or death was 1.92 per 1000 days of therapy in the non-target group, versus 0.85 per 1000 patient days in the target group (p<0.05).
CONCLUSION: Achieving target dosing with carvedilol can have a profound impact on medical resource utilization and mortality for patients with CHF. Unfortunately, only a minority of patients were titrated to the target dose of carvedilol.

13. Potential underutilization of spironolactone in patients hospitalized with heart failure. *Heather J. Tangeman, Pharm.D.,* Julie B. Cooper, Pharm.D. candidate, Kristen B. Campbell, Pharm.D. candidate, Amanda K. Garrand, B.A., Kirkwood F. Adams, Jr., M.D., J. Herbert Patterson, Pharm.D., FCCP; University of North Carolina, Chapel Hill, NC.

PURPOSE: We investigated spironolactone use in conjunction with standard heart failure (HF) therapy in patients admitted for decompensated HF. According to HFSA guidelines, administration of spironolactone at low doses (12.5-25 mg) should be considered in NYHA class IV patients admitted to hospital with systolic dysfunction (LVEF<35).
METHODS: From November 1, 2000 to April 20, 2001, we prospectively identified and recorded medication data for patients admitted with HF to cardiology units at a tertiary care, teaching hospital. Patients with newly diagnosed HF were excluded from analysis. Admission and discharge medications were documented from medical records and patient interviews.
RESULTS:

Clinical Characteristics (Mean)	No Severe LVD (NYHA II, III) LVEF >35% (N=31)	Severe LVD (NYHA III) LVEF <35% (N=65)	Severe LVD (NYHA IV) LVEF<35% (N=26)
LVEF	48.97	21.82	19.13
Male (%)	54.8	63.1	57.7
Age	63.6	61.06	53.9

LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction

Medications	No Severe LVD ADM/DC (%)	NYHA III ADM/DC (%)	NYHA IV ADM/DC (%)
Spironolactone	22.2 / 9.1	22.4 / 26.0	30.4 / 57.9
ACEI	74.1 / 88.0	75.9 / 81.0	91.3 / 87.5
BB	51.9 / 60.0	50.9 / 68.5	34.8 / 52.4
Digoxin	33.3 / 34.8	66.7 / 74.1	91.3 / 91.3
Furosemide	55.6 / 79.2	77.6 / 91.5	82.6 / 87.0

ADM = admit; DC = discharge; ACEI = angiotensin-converting enzyme inhibitor; BB = β-blocker

CONCLUSION: Spironolactone use appears to increase with the progressive severity of HF, yet may be underutilized in patients who might benefit most from it's known ability to reduce morbidity and mortality.

14. The self-reported Morisky score as a predictor of cardiovascular medication adherence. *Stephen J. Shalansky, Pharm.D.,* Adrian R. Levy, Ph.D., Richard Wanbon, B.Sc.Pharm., Gabriel Loh, B.Sc.Pharm., Roohina Virk, B.Sc.Pharm., Lisa Lui B.Sc.Pharm.; St. Paul's Hospital, Vancouver, BC, Canada; University of British Columbia, Vancouver, BC, Canada.

PURPOSE: To identify the extent to which interviewer-administered Morisky score identifies patients who are non-adherent with cardiovascular medications.
METHODS: The four-item Morisky scale was administered to patients who had taken cardiovascular medications for at least 3 months. One point was assigned for a positive response to each of the four questions. Adherence over the past 12 months was calculated based on fill dates and days supplied obtained from the British Columbia prescription database. Logistic regression was used to examine the association between the Morisky score (and its components) and non-adherence (<80%) with chronic cardiovascular medications, after adjusting for age, gender, number of prescription and OTC medications, reported adverse effects, and use of compliance aids.
RESULTS: Among 286 patients reporting Morisky scores, 36 (13%) were categorized as non-adherent. The mean Morisky score was significantly higher for non-adherent patients (1.3 ± 1.1 versus 0.7 ± 0.7, p=0.002) and was an independent predictor of non-adherence (OR 1.9, 95% CI 1.3-3.0, p=0.002).

Item	Non-Adherent Patients[a] (n=36)	Adherent Patients[a] (n=250)	Adjusted p value	Odds Ratio	95% CI
1. Do you ever forget to take your medicine?	61	39	0.01	1.7	0.8-4.0
2. Are you careless at times about taking your medicine?	28	22	0.47	0.9	0.4-2.3
3. When you feel better, do you sometimes stop taking your medicine?	11	1	0.01	2.8	0.4-17.5
4. Sometimes if you feel worse when you take your medicine, do you stop taking it?	31	6	<0.01	5.1	1.9-14.0
Yes to any item	81	52	0.02	3.3	1.3-8.1

[a] % answering Yes

CONCLUSION: Among patients with chronic cardiovascular conditions, the Morisky score is a significant predictor of non-adherence. However, patients are often misclassified which may limit the score's usefulness in a clinical setting.

15. Clinical pharmacists' impact on cholesterol management in patients with coronary artery disease. Tammy R. Lousberg, Pharm.D., BCPS, *Anne M. Denham, Pharm.D.,* Jane A. Kerzee, Pharm.D., John A. Merenich, M.D., FACP; Kaiser Permanente, Colorado Region, Denver, CO.

PURPOSE: Previous data has shown that of patients started on cholesterol-lowering therapy after a cardiovascular event, greater than 30% of patients stop therapy within one year. This study evaluates the ability of clinical pharmacists to manage patients long-term with established coronary artery disease after hospital discharge. It describes the number of patients who are maintained at their LDL goal and recidivism rates with cholesterol-lowering medications.
METHODS: The Clinical Pharmacy Cardiac Risk Service (CPCRS) focuses on medication management in patients with established coronary artery disease (CAD). Patients were identified using the Win!PTS (Merck and Co., Inc., 1999) database system. Electronic queries were completed to retrieve pertinent data. Most recent medication refill information was verified using pharmacy records.
RESULTS: There were 1339 patients followed by the CPCRS for greater than one year after hospital discharge. The mean age was 66 ± 10.3 years. The average length of follow-up was 648 days (1.8 years) ± 173 days (0.5 years). Ninety-five percent of patients had a low-density lipoprotein (LDL) cholesterol level checked within the past year. The LDL cholesterol was less than or equal to 130 mg/dl in 90% of patients and less than or equal to 100 mg/dl in 62% of patients. Eighty percent of patients had cholesterol-lowering medications filled within the past three months.

CONCLUSIONS: The latest Adult Treatment Panel III recommendations advocate a systems approach that includes collaboration with pharmacists to increase appropriate use of cholesterol-lowering medications. The results of this study endorse such an approach.

16. Utilization study of a cerivastatin conversion program within a United States Air Force primary care clinic. *Robin R. Feuge, Pharm.D., BCPS,* Mary Ann Halloran, Pharm.D., BCPS, Stephanie L. Anderson, Pharm.D.; University of Oklahoma, Oklahoma City, OK; Tinker Air Force Base, OK.

PURPOSE: The objectives of this study were to: 1) compare dyslipidemia control before and after a formulary conversion to cerivastatin; 2) determine the length of time after the conversion until measurement of the first fasting lipid profile (FLP) and liver function test (LFT); and 3) evaluate provider adherence to recommended dosing guidelines for this conversion program.
METHODS: Patients prescribed cerivastatin by Tinker Air Force Base providers were identified by a utilization report from October 1, 1999 to July 5, 2000. Medical records were selected for review using a random number generator. Patients were excluded if they used a statin for < 6 months prior to conversion or if cerivastatin was used for < 3 months during the study period.
RESULTS: The records for 46 patients were reviewed; of these, 89% were prescribed pravastatin and 11% were prescribed atorvastatin prior to the cerivastatin conversion. Forty-eight percent of patients pre-conversion versus 59% post-conversion met National Cholesterol Education Program ATP 2 (NCEP) goals for low-density lipoprotein (LDL; p=0.302). Mean ± SD for time to first FLP and LFT was 137 ± 78 days. Total cholesterol, LDL, and HDL were statistically improved after the conversion to cerivastatin. Providers followed dosing recommendations for the cerivastatin conversion 59% of the time.
CONCLUSIONS: Cerivastatin is as effective in reaching NCEP LDL goals compared to atorvastatin and pravastatin in this study population. The time to follow-up for FLP and LFT was longer than desired. Some providers deviated from the recommended dosing guidelines during this conversion program.

17. Population-based treat-to-target pharmacoeconomic analysis of HMG-CoA reductase inhibitors in coronary heart disease patients. B. Daniel Lucas, Jr., Cynthia A. Sanoski, Matthew K. Ito, Martha Aldridge, Judy W.M. Cheng, *Daniel E. Hilleman, Pharm.D.*; Creighton University, Omaha, NE.

PURPOSE: To conduct a population-based treat-to-target pharmacoeconomic analysis using the six commercially available HMG-CoA reductase inhibitors (statins). This analysis is designed to calculate the percentage of patients achieving LDL-C goals with each of the six commercially available statins and the cost of using each agent to treat the population.
METHODS: Baseline lipids were collected from 1773 patients with CAD and hypercholesterolemia not currently being treated with lipid lowering therapy. Treat-to-target results and cost was modeled using meta-analysis derived LDL-C lowering efficacy and AWP cost for different doses of each statin. In this model, the percentage of patients achieving the LDL-C target (≤ 100 mg/dl) with different doses of each agent was calculated. Patients not achieving goal at the highest dose of each agent were switched to a more effective statin. Patients requiring higher doses of each statin incurred the cost of repeat clinic visits and lipid panels (costs of health care services based on CPT-coding).
RESULTS: The median baseline LDL-C was 170 mg/dl. The percentage of patients reaching the LDL-C target with each statin was as follows: atorvastatin (A) 100%; cerivastatin (C) 50%; fluvastatin (F) 4%; lovastatin (L) 25%; pravastatin (P) 25%; and simvastatin (S) 89%. The average treatment cost per patient per year was: A $1267, C $1203, F $1327, L $1893, P $1803, and S $1577. Although C was associated with a total cost that was not significantly different from A, 50% of C treated patients required a switch to A to reach the target LDL-C. In addition, C use was associated with titration costs (clinic visits and lipid panels) that were more than double that of A.
CONCLUSION: Our economic model identified A and C as being more cost-effective than the other statins. However, C was capable of only achieving NCEP LDL-C goals in 50% of patients. As a result, this agent could not be used as the sole or primary statin agent in a closed formulary system.

18. Improving utilization of statins improves outcomes in CHD patients. *Daniel E. Hilleman, Pharm.D.,* Michael S. Monaghan, 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 heart disease (CHD) patients is erratic. We evaluated the effectiveness of a post-hospital discharge intervention prompting physicians to improve the utilization and effectiveness of statins in CHD patients.
METHODS: The control population included 303 consecutive CHD patients admitted to the coronary care unit of our teaching hospital from 10/01/98 through 12/31/98. The intervention group included 309 consecutive CHD 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 statin therapy (where appropriate) at 2, 8, 12, 24, and 52 weeks after hospital discharge. In addition, phone calls were made at 8, 12, 24, and 52 weeks after hospital discharge, where appropriate.
RESULTS: At hospital discharge, there was no significant difference in the utilization of statins between the groups. At 6 weeks and at each subsequent follow-up interval, the percentage of patients having lipid profiles determined, treated with a statin, receiving titrated doses of a statin, and achieving NCEP LDL-C goals was significantly greater in the intervention group compared to the control group. At the end of the 2-year follow-up interval, almost three-fourths of intervention patients were receiving a statin compared to less than one-half of the control group. In addition, 55% of intervention patients achieved their NCEP LDL-C goal compared to only 10% of the control patients. Recurrent myocardial infarction, hospitalization for myocardial ischemia, coronary revascularization, and cardiovascular mortality was significantly reduced in the intervention group compared to the control group ($p<0.05$).
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 drug doses. In addition, the improved utilization of statins significantly reduced the occurrence of adverse cardiovascular outcomes. This intervention tool should be more broadly applied in patient populations eligible to receive HMG-CoA reductase inhibitors.

19E. Endothelin-1 enhances tissue factor activity in human monocytes. *Tien M.H. Ng, Pharm.D.,* Kai I. Cheang, Pharm.D., Mark A. Munger, Pharm.D., Karleen S. Callahan, Ph.D., Edward M. Gilbert, M.D.; University of Utah Health Sciences Center, Salt Lake City, UT.

PURPOSE: It has been previously reported that monocyte tissue factor procoagulant activity (TF-PCA) is significantly elevated in heart failure subjects compared to age-matched healthy controls and that subjects exhibiting TF-PCA in the upper 50th-percentile were at increased risk of cardiac morbidity and mortality. However, the mechanism (s) for increased TF expression are unknown.
METHODS: To investigate a neurohormonal mechanism for increased monocytic TF expression in heart failure, TF-PCA was assessed in monocytes isolated from 18 healthy human volunteers and 18 symptomatic heart failure patients (NYHA FC II-IV) utilizing a one-stage recalcification assay. Monocytes were isolated using a standard Nycodenz® method. Isolated monocytes were stimulated with angiotensin II (AII), endothelin-1 (ET) and/or norepinephrine (NE). Tumor necrosis factor-alpha (TNFα) was used as the positive control.
RESULTS: Baseline monocyte TF-PCA was 2.5-fold higher in heart failure subjects compared to healthy normals (68.3 ± 104.3 vs 26.9 ± 35.1 TF units/μg protein, p=0.04). TF-PCA was induced 1.8-fold in the presence of ET in isolated healthy human monocytes (1.80 ± 1.55 fold difference in TF-PCA, p=0.04). However, ET failed to further increase TF-PCA in monocytes isolated from heart failure subjects. There was no induction of TF-PCA by either AII or NE.
CONCLUSIONS: The results of this study suggest ET, but not AII or NE, enhances TF activity in monocytes isolated from healthy individuals. ET stimulation does not produce any further effects on TF expression in monocytes isolated from heart failure subjects. ET may contribute to increased monocytic TF expression in heart failure.
Presented at the 2001 Annual Meeting of the Heart Failure Society of America, Washington, D.C., September 11, 2001.

20. A meta-analysis of interventions targeted at improving medication adherence in patients with hypertension. *Andrew M. Peterson, Pharm.D., BCPS,* Liza Takiya, Pharm.D., CDE, Rebecca Finley, Pharm.D., BCPS, MS, FASHP; University of the Sciences in Philadelphia; Philadelphia College of Pharmacy, Philadelphia, PA.

OBJECTIVES: The meta-analysis was designed to determine which types of interventions enhance medication adherence in hypertensive patients.
METHODS: A literature search from 1970 to December 2000 using Medline, PsychInfo, ERIC, IPA, and Embase was performed. Articles highlighting hypertension were manually identified. Inclusion criteria were: randomized, controlled, patient-directed interventions, with intervention groups containing more than 10 patients, and reporting sufficient compliance-related data.
RESULTS: Nineteen studies totaling 2446 patients were identified for analysis. Three articles had more than one intervention group, creating 24 intervention cohorts. Fourteen cohorts used behavioral (B) interventions (n=1531 patients), and 3 used educational (E) interventions (n=207 patients) and 7 cohorts used combined behavioral and educational (C) interventions (n=708). Meta-analysis was conducted using Systat software. ANOVA, Scheffe's test and the Q-test were used to determine statistical significance. Only the behavioral group of studies were found homogeneous (Q=1.2, 13 d.f., p=0.99). Using a random-effects model, the effect size (ES) for the B cohort was 0.04 (95% CI -0.01, 0.09, p=0.13). The ES were not different depending on study setting (p=0.13); 7 cohorts were studied in physician offices (ES=0.03) 3 in pharmacies (ES=0.06) and 4 in outpatient/LTC facilities (ES=0.09).
CONCLUSIONS: Although there exists a number of studies focused on

improving medication adherence in hypertensive patients, there seems to be little overall effect. Further studies need to be conducted to determine if educational interventions, or the combination of behavioral and educational interventions have an effect on medication adherence.

21. A meta-analysis of interventions targeted at improving medication adherence in patients with hyperlipidemia. *Liza Takiya, Pharm.D., CDE,* Andrew M. Peterson, Pharm.D., BCPS, Rebecca Finley, Pharm.D., BCPS, MS, FASHP; University of the Sciences in Philadelphia, Philadelphia, PA.

OBJECTIVES: The meta-analysis was aimed to (1) chronicle research targeted to improving medication adherence and (2) determine types of interventions that enhance medication adherence in hyperlipidemic patients.
METHODS: A literature search from 1970 to December 2000 using Medline, PsychInfo, ERIC, IPA, and Embase was performed. Articles highlighting hyperlipidemia were manually identified. Inclusion criteria were: randomized, controlled, patient-directed interventions, with intervention groups of a minimum of 10 patients, and reporting sufficient compliance-related data.
RESULTS: Five studies totaling 3077 patients were identified for analysis. One of the five studies had 3 separate interventions targeted at different cohorts of patients; therefore each intervention was considered a separate study, totaling 7 cohorts of patients. Five cohorts used behavioral interventions (n=2915), and two used both behavioral and educational (combined) interventions (n=162). Meta-analysis was conducted using Systat software. All cohorts were homogeneous based on the Q-test of homogeneity, (behavioral interventions p=0.26, combined interventions p=0.65, and all interventions p=0.29) and therefore could be aggregated for statistical purposes. Using a random-effects model, effect sizes for behavioral, combined, and all interventions were 0.14 (95% CI 0.10-0.19), p<0.01; 0.03 (95% CI -0.12-0.19), p=0.69; and 0.13 (95% CI 0.09-0.18), p<0.01, respectively.
CONCLUSIONS: Although there are limited studies focusing on improving medication adherence in hyperlipidemic patients, there seems to be a small but significant improvement when using behavioral interventions. Further studies need to be conducted to determine if educational interventions, or the combination of behavioral and educational interventions have an effect on medication adherence.

22. Pharmacodynamic profile of procainamide delivered into the pericardial space via percutaneous access. *Michael R. Ujhelyi, Pharm.D.,* Kelly Z. Hadsall, B.S., David Euler, Ph.D., Rahul Mehra, Ph.D.; Medtronic CRM Research and University of Minnesota, Minneapolis, MN.

INTRODUCTION: Procainamide (PA) delivered into the pericardial space exerts an electrophysiologic response specific to the atrium. This electrophysiologic effect was greatest at a cumulative pericardial PA dose of 3.5 mg/kg, however this study does not characterize a single dose effect nor does it mimic clinical care (i.e., open chest model). The current study goal was to fully characterize the safety and activity of pericardial PA in a clinically relevant close chested model prior to attempting first in human studies.
METHODS: Pericardial access was obtained in 5 domestic farm swine via percutaneous approach via femoral vein cannulation. A catheter was advanced into the right atrial (RA) appendage and advanced through the RA wall into the pericardial space. Pericardial access was documented via fluoroscopy with contrast injection and pericardial fluid aspirate demonstrating asanguinous fluid (hematocrit <2%). After baseline hemodynamic and RA endocardial effective refractory periods (ERP) were measured, all animals received a 2 mg/kg pericardial PA dose (10 ml) over 10 minutes with repeated ERP measurements and pericardial fluid sampling.
RESULTS: Table shows data from beginning of PA infusion (time=0) to resolution of ERP effect. The max RAERP prolongation was 22% (177 ± 12 to 216 ± 16 ms; p<0.01 vs T=0) and occurred at 48 ± 6 minutes. At T=90, the RAERP dissipated and retuned to baseline values at T = 180. There was no effect on mean arterial pressure (MAP) or heart rate (HR). Peak PA pericardial fluid concentrations were 1051 ± 152 ug/ml and was rapidly eliminated with an estimated T1/2 of 41 ± 2.1 minutes and VD 1.6 ± 0.16 ml/kg. Pericardial fluid NAPA concentrations never exceeded 3.5 ug/ml and neither PA nor NAPA were detected in serum samples.

Time (min)	RAERP ms	MAP mm Hg	HR bpm	PA ug/ml)
0	177 ± 12	89 ± 6	114 ± 7	0
10	192 ± 12	85 ± 4	115 ± 6	960 ± 47
20	193 ± 12*	88 ± 6	112 ± 6	954 ± 200
40	205 ± 13*	94 ± 7	110 ± 5	757 ± 140
60	208 ± 16*	91 ± 7	109 ± 6	665 ± 184
90	192 ± 14*	85 ± 6	109 ± 6	374 ± 82
120	188 ± 12	81 ± 5	106 ± 6	199 ± 39
150	185 ± 14	86 ± 6	108 ± 6	126 ± 23
180	177 ± 18	90 ± 10	109 ± 13	79 ± 14

CONCLUSIONS: Pericardial PA delivery has a unique pharmacokinetic profile that produces very high drug fluid concentrations at the local atrial affect site without systemic toxicity. This drug delivery strategy appears feasible in humans and may be ideal for acute atrial arrhythmia management via an implantable drug delivery system.

23. Achievement of National Cholesterol Education Program goal cholesterol levels in high-risk hyperlipidemic patients. Tracie R. Rothrock-Christian, Pharm.D., Julie Ann Gouveia-Pisano, Pharm.D., BCPS, Wendy A. Gattis, Pharm.D., BCPS; University of North Carolina, Chapel Hill, NC; Pfizer, Inc., Research Triangle Park, NC; Duke University Medical Center, Durham, NC.

PURPOSE: This study evaluated 1) the frequency of achieving National Cholesterol Education Program (NCEP) recommendations in patients with coronary artery disease (CAD) and/or diabetes mellitus, and 2) lipid management strategies between cardiology and general medicine services.
METHODS: A total of 69 dyslipidemic patients with CAD and/or diabetes mellitus admitted to Duke University Hospital between May 25 and August 13, 1999 were enrolled. Data was collected from personal interviews and medical chart reviews at the time of admission as well as three and six months after initial hospitalization. Patient characteristics included 34 (49.3%) male subjects and the mean age was 64.
RESULTS: At baseline, 29 (42.7%) patients met the NCEP-specified low density lipoprotein (LDL) goal of ≤ 100 mg/dl, and 33 (47.8%) reached this target during the 6-month follow-up. More patients treated by a cardiologist during follow-up met NCEP goals as compared to patients followed in a general medicine practice [23 (56%) vs 10 (36%)]. Thirty-six (52.2%) patients did not reach NCEP-recommended LDL cholesterol levels, and of these 45.7% had no change in drug therapy throughout the duration of the study.
CONCLUSIONS: NCEP guidelines for LDL cholesterol levels ≤ 100 mg/dl were achieved in less than half of patients with coronary artery disease and/or diabetes mellitus. The majority of these high-risk patients did not reach target LDL cholesterol levels, which suggests that many CAD and diabetic patients should be more aggressively managed regarding lipid-lowering therapy. Specific interventions are warranted with the goal of improving the use of evidence-based medicine.

24. Insulin induces endothelium-mediated vasodilation of mesenteric microvessels via the cyclooxygenase pathway. *Allison W. Miller, Pharm.D.,* Christina D. Tulbert, B.S., Michelle E. Puskar, B.S., David W. Busija, Ph.D.; Wake Forest University, Winston-Salem, NC.

Patients with insulin resistance have a greater incidence of hypertension. Alteration of insulin's vasoactive properties may link these diseases. Previous data show that insulin induces vasodilation in normal conduit arteries by enhancing nitric oxide (NO), however the mechanism of insulin-induced vasodilation in resistance arteries is unclear. Since resistance arteries are a greater determinant of blood pressure, we sought to determine insulin's effect on these arteries.
METHODS: Small mesenteric arteries (220 µM) were isolated from Sprague Dawley rats for assessment of vascular reactivity. Concentration-response experiments to insulin (0.1-100 ng/ml) in the absence and presence of inhibitors of cyclooxygenase (COX; indomethacin [INDO, 10 µM]), NO (N-nitro-L-arginine [LNNA 100 µM]), calcium-dependent K^+ channels (charybdotoxin [CTX, 100 nM] + apamin [500 nM]), ATP-dependent K^+ channels (K_{ATP}; glibenclamide [GLI, 10 µM]), or endothelium denudation (endo-) were performed in microvessels pre-constricted by 40% with phenylephrine. In addition, sections of mesentery were incubated in insulin (100 ng/ml) for 20 minutes in vitro and prostacyclin production was assessed by enzyme immunoassay.
RESULTS: Insulin induced a concentration dependent vasodilation that was abolished by INDO, GLI, and endo-, but unaffected by LNNA or CTX + apamin. For example, insulin alone induced a maximal relaxation of 49 ± 6%, however, in the presence of INDO, a slight vasoconstriction was elicited (-8 ± 5%). Moreover, insulin incubation of mesentery increased production of prostacyclin by 100% (6129 ± 894 pg/ml before versus 12,544 ± 1589 pg/ml after insulin, p<0.005).
CONCLUSIONS: These data provide functional and biochemical evidence that the COX pathway mediates insulin induced vasodilation of rat mesenteric resistance arteries through a K_{ATP} channel dependent mechanism

25. Evaluation of guideline therapy of rehospitalized patients with left ventricular systolic dysfunction. *Carmen S. Oitker, Pharm.D.,* Laura K. Smith, Pharm.D.; Mission St. Joseph's Health System, Asheville, NC.

PURPOSE: Strategies for treatment of congestive heart failure (CHF) are rapidly evolving and have resulted in revised guidelines. This study documented drug therapy in rehospitalized CHF patients in a private tertiary care hospital to 1) determine compliance with current guideline therapy, 2) determine presence of confounding medications, and 3) identify reasons patients are treated without recommended therapies.
METHODS: A retrospective review was performed on CHF patients rehospitalized within 31 days during fiscal year 2000. The data includes medications and education provided at initial discharge and at readmission.
RESULTS: Forty-five patients were included with an average ejection fraction of 23%. Readmission medications included ACE inhibitors (ACEI), β-blockers (BB), and spironolactone in 62% (n=28), 31% (n=14), and 22% (n=10) of patients, respectively. Lack of guideline therapy with absence of justifying documentation occurred in 13% (n=6), 74% (n=23), and 71%

(n=25) of patients with respect to ACEIs, BBs, and spironolactone. Renal insufficiency was a common reason cited for lack of ACEI and spironolactone. New diagnosis and hypotension were common reasons cited for lack of BB. Confounding medications were documented in 33% (n=15) of patients. Discharge patient instructions on sodium restriction and daily weights were documented in 60% (n=27) of patients.
CONCLUSION: Previous literature has shown underuse of ACEIs in CHF but presents little about why guidelines are not followed. This study documents reasons why both ACEIs and the newer therapies may not be utilized, and reemphasizes the importance of evaluating therapy and reinforcing discharge teachings.

26. Effectiveness and adverse reactions in patients treated with the new antiarrhythmic dofetilide. *Carmen S. Oitker, Pharm.D.,* Laura K. Smith, Pharm.D.; Mission St. Joseph's Health System, Asheville, NC.

PURPOSE: In 2000, a new class III antiarrhythmic, dofetilide, was released on the U.S. market. This study documented a private tertiary care hospital's dofetilide usage to 1) determine effectiveness during the initiation period, 2) determine incidence of complications, and 3) determine compliance with established protocols.
METHODS: A retrospective review was performed on all patients prescribed dofetilide between August 2000 and March 2001. The data includes prior antiarrhythmics, baseline lab data and cardiac function, dosing, QTc intervals, adverse reactions, and effectiveness at time of discharge.
RESULTS: Forty-eight patients were included in the study. Failure of previous antiarrhythmics occurred in 69% (n=33) of patients. Based on creatinine clearance, no patient exceeded the recommended initial dose of dofetilide. At discharge, 71% (n=34) of patients continued dofetilide, and the presenting arrhythmia was controlled in 71% (n=34) of patients. Dofetilide was effective in 61% (n=11) of 18 patients who had previously failed sotalol. After the first dose, the average increase in QTc from baseline was 5%. Dofetilide doses were decreased in 14.6% (n=7) of patients and discontinued in 8% (n=4) of patients due to prolonged QTc. Dofetilide was discontinued in 4% (n=2) of patients due to nausea and paroxysmal supraventricular tachycardia.
CONCLUSION: Dofetilide is touted to have nominal adverse effects apart from its potential to prolong the QT interval. During its initiation period, dofetilide appears to be an effective and well tolerated agent for many patients. No patient experienced torsades de points, but increased QTc did occur in this group and may be a limitation in the use of dofetilide.

27E. Vitamin C attenuates pacing-induced atrial electrical remodeling. *Cynthia A. Carnes, Pharm.D., Ph.D.,* Tomohiro Nakayama, DVM, Ph.D., Hitomi Nakayama, DVM, Ph.D., John A. Bauer, Ph.D., Robert L. Hamlin, DVM, Ph.D., David R. Van Wagoner, Ph.D.; Ohio State University, Columbus, OH; The Cleveland Clinic Foundation, Cleveland, OH.

Atrial electrical remodeling occurs during atrial fibrillation (AF). We tested the hypothesis that the antioxidant vitamin C (VC) would attenuate electrical remodeling during rapid atrial pacing (400 bpm), a canine model of AF.
METHODS: An electrode in the right atrial (RA) lateral free wall was used to measure atrial effective refractory period (aERP). A second RA electrode was used for pacing. The RA was paced for 48 hours (P1), allowed to recover, then repaced for 48 hours (P2). The baseline aERP was determined (BCL 300 msec) and after 1, 2, 4, 8, 24, and 48 hours of pacing. During P2 dogs were randomized to control or to VC (500 mg BID). The aERPs for each animal were normalized as a fraction of baseline.
RESULTS: Male beagles were studied. Baseline aERPs were 124 ± 9.4 msec in controls (n=5) and 120 ± 15 in the treatment group (n=6). In both groups, there was a significant time-dependent reduction in the aERP during P1 ($p<0.005$); the magnitude of the reduction was similar between the groups (p=NS). In the controls, there was no difference in the normalized aERP between the P1 and P2, indicating the stability of the preparations. In the VC group, there was a significant treatment effect on aERP during P2 ($P<0.043$), which reached significance at 24 and 48 hours of pacing ($p<0.05$). Fractional aERP (P2) are:

	Control Group	VC Group
24 hours	0.43 ± 0.07	0.77 ± 0.15
48 hours	0.40 ± 0.08	0. ± 0.14

CONCLUSIONS: This demonstrates that an antioxidant can modulate atrial electrophysiological remodeling during AF.
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28. Evaluation of compliance of dofetilide initiation protocol at the Cleveland Clinic Foundation. *Jodie M. Zalewski, Pharm.D.,* Michael A. Militello, Pharm.D.; Cleveland Clinic Foundation, Cleveland, OH.

PURPOSE: Dofetilide, a new class III antiarrhythmic agent for atrial fibrillation/flutter, prolongs the QT interval, thereby increasing the risk of drug induced torsades de pointes. In accordance with FDA mandated regulations, a Dofetilide Initiation Protocol has been developed at this institution to assure appropriate patient identification, dosing, and monitoring. The purpose of this drug use evaluation was to evaluate protocol compliance and determine dofetilide's safety.
METHODS: A chart review of patients initiated on dofetilide from May to November 2000 was performed. Patient demographics, renal function, baseline QTc interval, serum potassium, and drug interactions were evaluated to determine appropriate protocol compliance.
RESULTS: One hundred patients were analyzed. Complete protocol compliance was 77%. Compliance with baseline creatinine clearance and QTc interval was 89% and 88%, respectively. Subsequent monitoring and dose adjustment was also assessed. One contraindicated drug interaction with prochlorperazine occurred. A total of 21 patients experienced a ventricular arrhythmia, eight (8%) had no history of ventricular tachycardia. Two cases (2%) of torsades de pointes were documented, which is higher than the 0.8% incidence reported in dofetilide's package information. Protocol violations were present in 23 (23%) patients, of which, 8.7% (2/23) had a ventricular arrhythmia. Patients with protocol compliance had a 7.8% (6/77) rate of new ventricular arrhythmia.
CONCLUSION: A correlation between the incidence of ventricular arrhythmias and protocol non-compliance could not be identified. Although no increase in adverse events occurred in presence of protocol violations, the extent of adverse events is unknown in the absence of the protocol. Strict initiation guidelines are still prudent until more experience with dofetilide is documented.

29. A comparison of nadroparin and heparin in prophylaxis of thromboembolism after spinal surgery. Hyun-young Jung, M.S., Jee-Ho Lee, M.D., *Sukhyang Lee, M.S., Pharm.D.*; Graduate School of Clinical Pharmacy; Seoul City Boramae Hospital; Sookmyung Women's University, Seoul, Korea.

PURPOSE: Low molecular weight heparins (LMWHs) have been as effective in the prophylaxis and treatment as unfractionated heparin in orthopedic surgery with better profile of side effects. The purpose of this study was to evaluate efficacy and safety of nadroparin compared to heparin in prophylaxis of thromboembolism for spinal surgery.
METHODS: This retrospective study included patients on nadroparin (2850 IU SC once daily for 5 days) or heparin (5000 IU SC q12h for 7 days) after spinal surgery from June 1998 to May 2000 at Seoul City Boramae Hospital, Korea. Exclusion criteria were a history of thromboembolism or stroke within 6 months, spinal or eye surgery within 3 months, thrombocytopenia and active peptic ulcer disease. Data collection included demographic information, thromboembolism events, post–op ambulation time, clinical laboratory for platelet counts, hemoglobin, aPTT, and amounts of transfusion. Primary outcome was thromboembolism and bleeding events with evaluation of risk factors for 3 months postoperatively
RESULTS: Total 95 patients were included with 47 in the nadroparin group and 48 in the heparin group. All patients used compression stockings with mean age, 45.4 ± 14.1 years in the nadroparin vs 51.6 ± 15.7 years in the heparin; ambulation time, 8 days vs 9.3 days; weight 64.3 ± 9.7 kg vs 61.9 ± 10.4 kg. Thromboembolism event was very low with only 1 case in the heparin group, which was confirmed by Doppler sonography in the 62-year-old female. Bleeding complications were reported 4 cases in the heparin group with no cases in the nadroparin group. Number of patients with reduction of Hgb greater than 2 g/dl was 8 in the nadroparin group and 18 in the heparin group (p=0.025). Proportion of patients with Hgb reduction was the greatest in female older than 60 years among the subgroup combinations by sex (male vs female) and age (>60 or <60 years; p=0.003). Thrombocytopenia was identified 7 in the heparin group with no cases in the nadroparin group.
CONCLUSION: Nadroparin and heparin was effective and similar in prophylaxis of thromboembolism after spinal surgery but heparin had more incidence in bleeding events, reduction of Hgb and thrombocytopenia. Nadroparin can be used in place of heparin as anticoagulation therapy for patient with high risk of bleeding complications. Cost-effectiveness for anticoagulation therapy should be evaluated further for patients with risk of thromboembolism after spinal surgery.

30. Evaluation of the use of β-blockers in congestive heart failure in a VA medical center: a retrospective DUE. *Andrew J. Smith, Pharm.D.,* Douglas R. Geraets, Pharm.D.; VA Medical Center, Iowa City, IA.

PURPOSE: Beta-blocker use significantly reduces both morbidity and mortality associated with congestive heart failure (CHF). The specific aims of this study were: 1) assess whether β-blockers are appropriately utilized in the treatment of CHF and 2) examine predictors of β-blockers underutilization among CHF patients.
METHODS: A retrospective cohort chart review was performed. Use criteria in CHF were based on recently published guidelines. Patients with CHF were identified through ICD-9 codes and left ventricular ejection fractions (LVEF) <40%. Pharmacy data were used to identify patients receiving β-blockers, angiotensin converting enzyme inhibitors and diuretics. Populations were cross-referenced to produce a list of patients with heart failure and who were and were not receiving β-blockers. Demographic and treatment variables of the groups were compared to explore predictors of underutilization.
RESULTS: Metoprolol (15/30; 50%), was the most common β-blocker used followed by atenolol (12/30; 40%) and carvedilol (3/30; 10%). Functional class was documented in only 13 percent of patients. On average patients

were initiated on greater than twice the recommended starting doses, and titrated to only seventy percent of target doses. Average baseline LVEF in the β-blocker group was higher than the group not on β-blocker (37% vs 30%, p=0.02). The groups did not differ in regards to concurrent disease states, primary care providers or enrollment in cardiology clinic.
CONCLUSIONS: β-Blockers are not being used in full accordance with national guidelines. Areas for improvement include smaller starting doses and better completion of dosage titration. Lower LVEF may be a predictor of underutilization of β-blockers.

31. Use of acetylcysteine in patients with renal insufficiency prior to cardiac catheterization. *Paul P. Dobesh, Pharm.D.,* Sara L. Schroeder, Pharm.D., Jonathan E. Lakamp, Pharm.D.; St. Louis College of Pharmacy; St. Louis, MO; St. Luke's Hospital; Chesterfield, MO.

PURPOSE: Recent literature has shown acetylcysteine to prevent the reduction in renal function induced by contrast agents in patients with renal insufficiency undergoing computed tomography. At our institution, acetylcysteine is being used in a similar fashion in patients undergoing cardiac catheterization (CC). We performed a retrospective analysis of acetylcysteine's ability to provide similar protection in this patient population.
METHODS: Patients undergoing CC receiving acetylcysteine between 7/00-5/01 were included. Only patients with preexisting renal insufficiency (Serum creatinine [SrCr] > 1.2 mg/dl or CrCl < 50 ml/min) were evaluated. SrCr was collected at baseline, 24-hours, and 48-hours. Acetylcysteine dose, fluid administration, concurrent drugs and amount/type of contrast were evaluated.
RESULTS: Patient demographics were similar to results previously published. Thirty-one patients (65% diabetics) met inclusion/exclusion criteria. Seventy-seven percent of patients received an appropriate dosing regimen of acetylcysteine. The mean SrCr concentration was 2.3 mg/dl at baseline and 2.2 mg/dl 48 hours after administration of contrast (p=NS). Two patients (6.5%) had an increase of at least 0.5 mg/dl in the SrCr at 48 hours. All but one patient received non-ionic contrast (mean 84.5 ml) exclusively.
CONCLUSIONS: Prophylactic oral administration of acetylcysteine may help to prevent the reduction in renal function commonly seen after the administration of intravenous contrast. A randomized, prospective study comparing the administration of acetylcysteine to placebo in patients undergoing CC is warranted. Until that is performed, oral acetylcysteine appears to be a safe and inexpensive approach, and may provide benefit when used prior to administration of non-ionic contrast in patients undergoing CC.

32. Cardiovascular effects of cocaine and cocaethylene in the conscious dog. *Robert B. Parker, Pharm.D.,* Naomi Gades, DVM, Timothy Mandrell, DVM, S. Casey Laizure, Pharm.D.; University of Tennessee; St. Jude Children's Research Hospital, Memphis, TN.

PURPOSE: The cardiovascular effects of cocaine (Coc) and cocaethylene (CE), the active metabolite of cocaine formed only when cocaine is co-ingested with ethanol, have previously been reported in anesthetized dog models. However, general anesthesia attenuates many of the cardiovascular effects of Coc and CE confounding interpretation of the results. The present study compares the cardiovascular effects of Coc and CE in conscious dogs.
METHODS: Six male, adult, conditioned, mongrel dogs received 5 mg/kg Coc or CE as a 5-minute IV infusion with continuous monitoring of the ECG and arterial blood pressure. Arterial blood samples were collected at baseline and 3, 5, 7, 10, 15, 20, 35, 65, 125, and 185 minutes after the start of the infusion. Coc and CE plasma concentrations were determined by HPLC. A simple Emax pharmacodynamic model was used to evaluate the relationship between the heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), rate-pressure product (heart rate X SBP), QRS duration, QTc interval, PR interval and plasma concentrations of Coc and CE. Estimates of Eo (baseline effect), EC_{50}, and Emax, and the maximum change (Max Chg=Observed maximum effect-Baseline value) were compared using the Mann-Whitney Test.
RESULTS: The table gives the mean±standard deviation for the parameter estimates from the Simple Emax model [E=Eo+ (Emax-Eo)X (C/ (C+EC50))] that was fitted to the data. Significant differences in EC_{50} for SBP (Coc<CE) and QRS duration (CE<Coc) were observed. The Max Chg for QRS duration and PR interval was significantly greater for CE than for Coc. The peak plasma concentrations for Coc and CE were 4774±1230 and 5570±1218 ng/ml, respectively (p=0.64).

	Cocaine			Cocaethylene			Max Chg	
	Eo	EC_{50} (ng/ml)	Emax	Eo	EC_{50} (ng/ml)	Emax	Cocaine	CE
HR (beats/min)	102 ± 6	4318 ± 2215	191 ± 40	101 ± 8	8812 ± 11274	205 ± 122	50 ± 35	53 ± 28
SBP (mm Hg)	152 ± 12	545 ± 224	248 ± 20	158 ± 15	1878 ± 1802†	265 ± 43	85 ± 50	79 ± 32
DBP (mm Hg)	86 ± 12	1133 ± 653	178 ± 17	74 ± 14	1485 ± 822	176 ± 23	73 ± 40	75 ± 21
QRS (msec)	62 ± 4	7327 ± 9453	110 ± 33	62 ± 9	952 ± 729‡	95 ± 9	19 ± 12	29 ± 9†
QTc (msec)	316 ± 8	16538 ± 10595	499 ± 99	297 ± 20	6349 ± 13890	370 ± 51	35 ± 31	88 ± 64
PR (msec)	119 ± 11	5765 ± 9874	125 ± 29	113 ± 12	6971 ± 14213	179 ± 104	18 ± 13	32 ± 16†
RPP (mm Hg x beats/min)	156 ± 21	1487 ± 871	408 ± 105	160 ± 22	9227 ± 12799	570 ± 327	211 ± 148	181 ± 59

† value for CE is significantly greater than Coc ($p < 0.05$); ‡ value for Coc is significantly greater than CE ($p < 0.05$)

CONCLUSIONS: Previous reports of CE cardiovascular effects in anesthetized dogs have demonstrated dose-dependent decreases in BP with minimal effects on HR. In contrast to these results in an anesthetized model, our data in conscious animals with an intact autonomic nervous system indicate Coc and CE significantly increase BP and HR. Coc and CE have similar cardiovascular effects. However, CEs lower EC_{50} and greater Max Chg for QRS duration indicates it is a more potent sodium channel blocker than Coc. CE contributes to cardiovascular toxicity when Coc and ethanol are co-ingested.

33. β-blocker use in a population of veterans with heart failure. *Mark C. Granberry, Pharm.D.,* Jason B. Hawkins, Pharm.D., Amy H. Franks, Pharm.D., Eugene S. Smith, III, M.D.; University of Arkansas for Medical Sciences, Little Rock, AR; Central Arkansas Veterans Healthcare System, Little Rock, AR.

PURPOSE: Beta-blockers are considered standard therapy for heart failure patients with ejection fractions ≤ 40% as these drugs are known to prolong survival and reduce hospitalizations. The optimal agent and dose has not been determined however, the drugs used and doses achieved in the clinical trials are generally recommended. We sought to determine the utilization rates and dosages of β-blockers in these patients.
METHODS: A retrospective observational study design was used. Patients were included if they were treated at the Central Arkansas Veterans Healthcare System from 10-1996 through 3-2001, had a heart failure diagnosis and a documented ejection fraction of ≤ 40%. Medical records were reviewed to determine β-blocker utilization rates and "target doses" defined as: carvedilol ≥ 50 mg daily, metoprolol immediate-release (IR) and metoprolol extended-release (XR) ≥ 150 mg daily.
RESULTS: Of 529 patients who met inclusion criteria, 134 patients died or were otherwise unable to be evaluated, thus 395 patients were evaluated for β-blocker therapy. Of these, 262 patients (66%) were currently treated with β-blockers; 114 with carvedilol (47.4% at or above target), 30 with metoprolol XR (30% at or above target), 84 with metoprolol IR (15.5% at or above target), and 34 with other β-blockers.
CONCLUSION: A high number of patients were treated with β-blockers with the majority on carvedilol and metoprolol. Target dose was achieved more frequently in patients treated with carvedilol, followed by metoprolol XR and lastly metoprolol IR. Factors associated with less than optimal β-blocker use will be determined and appropriate actions taken.

34. Impact of a pharmacist-managed patient assistance program (PAP) on uncontrolled blood pressure (BP) in an indigent population. *Peter Dumo, Pharm.D.,* Paul Sobotka, M.D.; Harper University Hospital; Detroit Medical Center and Department of Pharmacy Practice; Wayne State University, Detroit, MI.

PURPOSE: Many patients have difficulty coping with the rising number and cost of medications required for their multiple co-morbidities. Some health-care providers have turned to pharmaceutical manufacturers' drug assistance programs in order to improve medication access for these patients. The purpose of this study is to determine if improved medication access through a pharmacist-managed PAP improves BP control in these patients.
METHODS: Patients identified as requiring assistance were enrolled into the PAP. All medications conveniently available through manufacturers' assistance programs were provided by the pharmacist-managed PAP. BP was on the first visit and from subsequent clinic visits. The patient's initial medication regimen was also documented. Patients with an initial BP above their JNC-VI goal were included in this study. Baseline BP was compared with the average BP recorded while participating in the PAP using the paired t-test.
RESULTS: The average age of participants in this program was 67 years old with 2/3 being Medicare recipients. Twelve of 27 patients were male.

	Before Assistance	During Assistance	p-value
Systolic BP	163 ± 28	146 ± 24	0.013
Diastolic BP	86 ± 13	79 ± 12	0.035
Patients Achieving JNC-VI goals	0%	11/27	<0.001

CONCLUSIONS: Indigent patients with poorly-controlled BP participating in a pharmacist-managed PAP experience significant reductions in both systolic and diastolic BP. Based on the data collected, it is not possible to determine if these improvements result from improved access, greater number of antihypertensive medications prescribed, patient education via the pharmacist administering the program, or a combination of all 3 factors.

35. Adherence to acute myocardial infarction treatment guidelines and clinical outcomes. *Surakit Nathisuwan, Pharm.D., BCPS.,* Robert L. Talbert, Pharm.D., FCCP, BCPS; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX.

PURPOSE: To assess adherence to national treatment guidelines for acute myocardial infarction (AMI) during and up to 1 year after hospitalization.
METHODS: Medical records and complete prescription records for all AMI patients for 1999-2000 were reviewed. Demographic, diagnostic and pharmacotherapy variables were collected. The relationships between medication use, lipid goals and major adverse cardiovascular events (MACE: death, recurrent MI, stroke, need for revascularization and hospitalization for cardiac reasons) were examined.
RESULTS: Medical records for 96 patients met review criteria. Mean (±SD) age, SBP, DBP and HR were 57.8±10.1 year, 135.9 ± 27.4 mm Hg, 73.3 ± 15.3

mm Hg, and 79.3 ± 19.3 bpm, respectively. Median glucose, troponin peak, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride were 175.0 mg/dl, 12.9 ng/ml, 178.5 mg/dl, 105 mg/dl, 40 mg/dl, and 170 mg/dl, respectively. The mean length of stay was 8.5±5.1 days. Aspirin, nitrates, β-blockers, heparins, glycoprotein IIb/IIIa inhibitors and ACEI were prescribed to 100%, 98.9%, 92.7%, 97.9%, 62.5% and 62.5% of patients during the hospitalization, respectively. During a 12-month follow-up, patients achieving LDL-cholesterol <100 mg/dl at 3 months had fewer MACE (p=0.039). Patients on ACEI in-hospital or at discharge and at ≥2 follow-up periods were less likely to have MACE (14 vs 28 events, p=0.04). Reduced hospitalization accounted for most of the event reduction (9 vs 20, p=0.0003).
CONCLUSIONS: Compliance to guidelines at this center exceeds that of average rates reported by national practice surveys. Achieving lipid goals and use of ACEI resulted in fewer MACE.

36. Antiplatelet agents improve survival in patients with heart failure: a meta-analysis. *Paul E. Nolan, Jr., Pharm.D.,* Marion K. Slack, Ph.D., Christy M. Evans, Pharm.D.; University of Arizona, Tucson, AZ.

PURPOSE: Heart failure (HF) may confer a hypercoagulable state secondary to abnormal blood flow, endothelial dysfunction or platelet activation. However, it remains uncertain whether antiplatelet agents (APA) improve survival in patients with HF. The purpose of this study was to evaluate the use of APA in patients with left ventricular systolic dysfunction (LVSD) ± symptoms of HF.
METHODS: MEDLINE searches were performed from 1966 to June, 2001. Clinical trials enrolling patients with documented LVSD ± symptoms of HF and reporting mortality results and patients' use of APA were identified. In addition, studies had to be prospective, randomized controlled trials (RCTs), retrospective analyses of previously reported RCTs, or cohort studies. Using meta-analytic methods, mortality outcomes for APA users and non-users were aggregated and compared to estimate odds ratio and confidence intervals.
RESULTS: Four studies met inclusion criteria and these were retrospective analyses of RCTs (3) or cohort studies (1). Aspirin was the APA used in >95% of patients. There were 27,123 total patients evaluated: 16,951 APA users and 10,172 APA non-users. Etiology of LVSD ± symptoms of HF was predominantly ischemic (nearly 95% of patients). There were 3304 deaths (19.5%) in the APA users group compared to 2925 (28.8%) in the APA nonusers group (OR: 0.65, 95% CI: 0.61 - 0.69, p<0.0001).
CONCLUSION: These results suggest that APA (i.e., aspirin) use in patients with LVSD ± symptoms of HF secondary to an ischemic etiology significantly decreases mortality. This survival benefit is independent of concomitant use of angiotensin-converting enzyme inhibitors.

37. Optimizing hypertension outcomes through "best practice" standards within AvMed Health Plan. *James H. Jackson, IV, Pharm.D.,* Prashant T. Nikam, M.S., Bruce Weiss, M.D., M.P.H.; Applied Health Outcomes, Tampa, FL; AvMed Health Plan, Gainesville, FL.

PURPOSE: Hypertension (HTN), a significant and disabling illness affecting 50 million Americans, is associated with morbidity and premature mortality. Patients with HTN and comorbid conditions are at even higher risk. Recognizing the detrimental effects of uncontrolled HTN, AvMed Health Plan implemented a comprehensive HTN quality improvement program. The program followed recommendations from the Sixth Report of the Joint National Committee (JNC-VI) guidelines for management of high blood pressure (BP). It included three phases: Baseline Assessment, Intervention, and Follow-up Assessment.
METHODS: Patients receiving antihypertensive agents between June 1, 1998 - May 31, 1999 (Baseline) and October 1, 1999 - September 30, 2000 (Follow-up) were included. During baseline and follow-up, approximately 500 patients were randomly selected for medical chart review to assess BP control, comorbid conditions, and risk factors. The intervention phase (September 1999 - April 2000) included physician-focused interventions such as Physician Report Cards, Physician Newsletters, and Educational Seminars that emphasized compliance with JNC-VI guidelines.
RESULTS: The study findings demonstrated significant improvement in BP control (p=0.0004), using a standard of <140/90 mm Hg (baseline 41.1%; follow-up 52.0%) and improved compliance with "Best Practice" measures, as defined by JNC-VI guidelines. Follow-up results showed a significant increase in diabetic hypertensive patients receiving an ACE-Inhibitor (47.2% vs 49.4%, p<0.0001). Additionally, there was a significant increase in post-MI hypertensive patients receiving β-blockers and CHF hypertensive patients receiving ACE-Inhibitors or ARBs (45.3% vs 47.0%, p=0.0144 and 48.6% vs 52.2%, p<0.0001, respectively).
CONCLUSION: Through provider-focused quality improvement programs, compliance with nationally- recognized guidelines for HTN management and patient BP control can be improved.

38. Identification of bleeding complications by coding data in patients undergoing percutaneous coronary intervention and/or stent procedure. *Mark A. Parmenter, Pharm.D.,* Vikas Gupta, Pharm.D., BCPS; Scripps Health, San Diego, CA; Owen Healthcare, Inc., Houston, TX.

PURPOSE: Other than controlled trials, there is little data on the bleeding rates in patients treated with percutaneous coronary intervention (PCI) ± stent procedure from community hospital setting. The purpose of this evaluation was to identify bleeding rates associated with PCI in a community hospital using coding data.
METHODS: The following information was obtained from the Scripps Trendstar® database for DRGs 112 (PCI) and 116 (PCI + stent procedure) from October 1,1999 to September 30,2001 for Scripps Memorial Hospital in La Jolla, CA; all procedure and diagnosis codes. From this group, patients with bleeding complications, glycoprotein 2B3A inhibitors (GPI) use and/or transfusion therapy were identified.
RESULTS: A total of 1,584 (93.6%) of 1,692 patients were coded for PCI±stent procedure. Using standard ICD-9 coding definitions, 107 patients (6.7%) were coded for a bleeding complication, included 24 with post hemorrhagic anemia, and 35 with hemorrhage. Transfusions were given to 55 (3.5%) of the patients of which 31 were coded for a bleeding complication while 24 were not. If all patients that received transfusions were included in the bleeding complications group, the overall-bleeding rate would be 8.3%. A GPI was administered in 71% of patients coded for bleeding complications vs 47% that were not coded for bleeding complication.
CONCLUSION: This coding analysis of PCI ± stent procedure identified a bleeding rate of 8.3%, which is similar to that reported in the literature. Such an analysis may assist other institutions in identifying their bleeding complication rates. A clinical evaluation is underway.

39. Decreased postoperative bleeding with albumin vs hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of randomized trials. *Mahlon M. Wilkes, Ph.D.,* Roberta J. Navickis, Ph.D., William J. Sibbald, M.D.; Hygeia Associates, Grass Valley, CA; University of Toronto, Toronto, ON, Canada.

PURPOSE: To test by meta-analysis the hypothesis that cumulative blood loss during the first 24 h after cardiopulmonary bypass surgery is lower in patients exposed to albumin than hydroxyethyl starch (HES).
METHODS: Randomized controlled trials comparing albumin and HES in cardiopulmonary bypass patients were identified by bibliographic database searches, hand searching of journals, inquiries with randomized trial investigators and medical directors and examination of reference lists. Trials were selected and data extracted independently by two investigators.
RESULTS: Sixteen trials with a total of 653 randomized patients were included. In 88% of randomized comparisons postoperative bleeding was lower in the albumin group, and the standardized mean difference (SMD) in bleeding across all trials (-0.24; 95% CI, -0.40 to -0.08) was statistically significant. Significantly less bleeding was observed in the albumin group both among the 11 trials investigating volume expansion (SMD, -0.21; 95% CI, -0.39 to -0.02) and the 5 trials of pump priming (SMD, -0.32; 95% CI, -0.61 to -0.03). Bleeding differences were similar between albumin and either high or medium molecular weight HES. Among the 14 trials of adults, pooled mean blood loss in the albumin group was 693 ± 350 ml compared with 789 ± 487 ml in HES recipients, and the estimated proportion of adult albumin group patients with blood loss > 1000 ml was 19% compared with 33% of adult HES group patients.
CONCLUSION: Fluid management with albumin results in significantly lower postoperative blood loss among cardiopulmonary bypass patients as compared with HES.

40. Evaluation of drug costs for patients with ACS managed with and without percutaneous cardiac intervention. *Vikas Gupta, Pharm.D., BCPS,* Mark Parmenter, Pharm.D., Juanita Hill, Pharm.D.; Owen Healthcare, Inc., Naperville, IL; Scripps Health, San Diego, CA; Cardinal Health Provider Pharmacy Services, Houston, TX.

PURPOSE: Given the recent advances in management of patients with acute coronary syndrome (ACS), there is little information comparing drug costs of patients managed with or without percutaneous cardiac intervention (PCI). The purpose of this evaluation is to compare drug costs and length of stay (LOS) of these two management strategies in a community hospital health system.
METHODS: The following information was evaluated from Diagnosis Rx™ (Cardinal Health Provider Pharmacy Services, Houston, TX) for DRGs 112, 116, and 121-123 from March 1, 2000 to March 1, 2001 for Scripps System in San Diego, CA: total drug costs, patient days, drug costs per patient day, discharges, and cost per discharge. Patients with ACS managed by PCI were evaluated for DRGs 112 and 116 and without PCI for DRGs 121-123. Results include the average (± SD) of the 5 institutions evaluated.
RESULTS: Total of patient days (8850 vs 5575) and discharges (4053 vs 1130) were higher for PCI vs without PCI, respectively. However, average LOS was lower PCI (2.18 ± 2.48 days) vs without PCI (4.93 ± 0.89 days). Total drug costs when evaluated by patient day were higher for PCI ($211 ± $97) vs without PCI ($145 ± $46). However, total drug costs by discharge were higher without PCI ($714 ± $315) vs with PCI ($460 ± $338).
CONCLUSION: This analysis shows that total drug costs are lower for patients managed by PCI than without PCI. Such an analysis may assist health systems in developing ACS management strategies to manage drug costs without compromising clinical outcomes.

41. The effect of rosiglitazone therapy on serum cholesterol levels. *David A. Bookstaver, Pharm.D.*; Eisenhower Army Medical Center, Fort Gordon, GA.

PURPOSE: Rosiglitazone (ROSI) has been shown to affect lipoprotein levels in randomized clinical trials. This study assessed the effect of ROSI therapy on the lipid profile during clinical practice.
METHODS: Medical records of patients prescribed ROSI between July 1, 1999 and March 31, 2001 were reviewed. Patients were included in the analysis if they had a lipid profile determination within 6 months before and between 2 and 6 months after drug initiation. Additionally, patients were required to have been on a stable dose of a lipid-lowering medication if one was prescribed.
RESULTS: One hundred forty five patients met inclusion criteria. ROSI therapy was associated with a significant increase in mean (± SD) total cholesterol, HDL and LDL levels. No dose relationship to effect was shown upon comparing 4 and 8 mg daily.

	Total Cholesterol	Triglycerides	HDL	LDL
Total n Baseline	191 ± 41	240 ± 187	46 ± 14	104 ± 35
Total n Follow-up	209 ± 55	248 ± 208	48 ± 15	113 ± 36
p	< 0.001	0.54	0.0007	0.003
4 mg Baseline	194 ± 42	249 ± 187	45 ± 12	107 ± 35
4 mg Follow-up	213 ± 60	281 ± 243	47 ± 12	113 ± 39
8 mg Baseline	185 ± 41	243 ± 206	46 ± 14	97 ± 32
8 mg Follow-up	203 ± 47	220 ± 152	49 ± 16	116 ± 36
p	0.20	0.31	0.53	0.64

CONCLUSION: The results are consistent with those shown during clinical trials; however, the magnitude of changes in HDL and LDL were lower. The clinical significance of the LDL elevation is dependent upon the outcome of studies investigating the effect of ROSI on LDL particle size.

42. The use of ambulatory blood pressure monitoring to influence drug regimens in a hypertension specialty clinic. *Kristi W. Kelley, Pharm.D.,* Deborah S. King, Pharm.D., Marion R. Wofford, M.D., MPH, Sharon B. Wyatt, Ph.D., RN, CANP, Daniel W. Jones, M.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: Ambulatory blood pressure monitoring (ABPM) has been effectively used in clinical trials to assess response to antihypertensive therapy. Despite its potential usefulness, evidence is needed to demonstrate ABPM's utility in clinical practice.
METHODS: Clinic records and ABPM data of all patients undergoing 24-hour ABPM between June 1, 1999 and May 31, 2000 (n=43) were evaluated. Data collection included in-clinic blood pressures obtained using a mercury sphygmomanometer (BPHg), ABPM results using SpaceLabs equipment, a medication history and profile, and reasons for ABPM. Records were analyzed to determine the influence of ABPM on pharmacotherapeutic decisions.
RESULTS: The majority of ABPMs were performed to assess uncontrolled hypertension (33%) or suspected secondary hypertension (23%). Using a paired t-test, mean arterial blood pressure (MAP) from clinic BPHg was compared to ABPM. No significant differences between clinic BPHg and daytime ABPM MAP (p=0.888) or Total 24-hour ABPM MAP (p=0.877) were found. However, significant differences were noted between day and night ABPM MAP (p<0.0001) as well as day and total 24-Hour MAP (p<0.0001). Inadequate control of in-clinic BPHg was noted in 67% of patients (mean BP > 140/90), compared to inadequate control in 49% with ABPM (mean BP > 135/85). These comparisons were useful for making therapeutic interventions including changing medications (44%) or maintaining current regimens (35%).
CONCLUSIONS: ABPM is useful for evaluating blood pressure control and the appropriateness of pharmacotherapy. This preliminary data supports the utility of ABPM for optimal hypertension management in selected patients.

43. Assessment of the awareness of obesity and blood pressure as cardiovascular risk factors in a historically African-American university. *T. Kristopher Harrell, Pharm.D.,* Nancy N. Horton, Ph.D., MPH, Deborah S. King, Pharm.D., Marion R. Wofford, M.D., MPH, Annette K. Low, M.D., Sara L. Noble, Pharm.D.; University of Mississippi Medical Center; Jackson, MS.

PURPOSE: Mississippi has the highest overall cardiovascular (CVD) mortality rate in the nation. While overall CVD mortality rates have been declining, Mississippi African-American rates of death have not been improving at the same rate. Little information is available for younger Americans, especially African-Americans. The purpose of this study was to assess the awareness of obesity and hypertension in students attending a historically African American university.
METHODS: An initial survey was conducted on the university campus to evaluate knowledge of health status. Students were asked to complete a series of cardiovascular health questions, and were then measured for height, weight, and blood pressure. Outcome measures included correlation between perceived height and weight versus actual height and weight, prevalence of hypertension, prevalence of obesity, and awareness of goals for BMI and blood pressure.
RESULTS: A total of 145 students completed the survey. Correlation coefficients between self-reported and actual heights and weights were 0.96 and 0.97, respectively. Average BMI was 26.59, and 32 (22%) students had a BMI of ≥ 30. Eighty-one (56%) students were considered overweight or obese (BMI≥25). Mean systolic and diastolic blood pressures were 122.7 mm Hg and 73.7 mm Hg, respectively. A total of 21 (14%) students reported knowing blood pressure goals, while only 3 (2%) students reported knowing BMI goals.
CONCLUSIONS: This study demonstrated good correlation between students' perceived and actual heights and weights. It also identified the need to increase awareness of blood pressure and BMI goals among students at this historically African American university.

45. Does delivery of care influence carvedilol use in clinical practice? *Lisanne DiTusa, Pharm.D.,* Melissa Butler, Pharm.D., William Carlson, M.D., Brian Snyder, M.D., Aileen B. Luzier, Pharm.D.; Massachusetts College of Pharmacy and Health Sciences, Boston, MA; Harvard Medical School, Boston, MA; Harvard Vanguard Medical Associates, Boston, MA; Univera Healthcare, Buffalo, NY; University at Buffalo, Buffalo, NY.

Titration of carvedilol to a target dose of ≥ 50 mg daily has proven benefit in patients with heart failure. We evaluated titration and tolerability of carvedilol in two managed care environments with different approaches directing titration, usual care (UC) versus specialized clinic (SC). We reviewed the medical records of all patients with a diagnosis of heart failure receiving carvedilol for ≥ 2 months. Demographic and clinical data were documented at the start of carvedilol therapy and at highest stable dose achieved. Chi-square and Kruskal-Wallis were used to compare utilization and titration schedules. Of the 119 patients evaluated, mean age 64 (± 13) and 35% males, 27% reached target dose with average titration period of 7 (± 8) months and discontinuation rate of 24%. Site-specific analysis showed:

	UC	SC
Number of Patients	59	60
Achievement of Target Dose*	11 (19%)	21 (35%)
Titration Period (months)*	3.4 (± 4.5)	9.6 (± 9.5)
Discontinuation Rate	11 (19%)	18 (32%)

* p<0.05 UC vs SC

Elderly patients (>65 y/o) received target doses less often than younger patients (15% vs 38%, p<0.01) and did not differ between sites. Systolic blood pressure <110 mm Hg and heart rate <60 bpm was documented in 33% and 9% of patients, respectively, and did not differ with dose or site.
CONCLUSION: In the clinical practice setting, discontinuation rates of carvedilol are higher, titration is slower, and achievement of target dose is less frequent compared to clinical trial data. Although improved utilization was observed in the SC setting, efforts to improve the clinical use of carvedilol are warranted.

46. Challenges in maintaining patients with coronary artery disease at LDL-cholesterol target. *Lisanne DiTusa, Pharm.D.,* Maureen Welch-Costantino, R.N., Maribeth Taylor, Kristen Oberg, Pharm.D., William Carlson, M.D.; Massachusetts College of Pharmacy and Health Sciences; Harvard Medical School; Harvard Vanguard Medical Associates, Boston, MA.

We prospectively evaluated low density lipoprotein cholesterol (LDL-C) levels in patients with coronary artery disease (CAD) who completed a controlled focused care (FC) cholesterol-lowering trial to determine the number of patients that achieve and maintain LDL-C target over a 1 year period. Through computerized medical records we identified a similar group of patients receiving usual care to serve as the control group. We recorded LDL-C levels at baseline, lowest achieved and at follow-up. The cumulative number of patients that achieved LDL-C targets ≤100, <105 and <110 mg/dl was documented. Medication dose was recorded at lowest LDL-C level and at 1- year.
RESULTS: Overall, significantly more FC patients achieved target and there was a trend for FC patients to receive higher doses of medication. Additionally, in the FC group there was 16 patients that achieved target during the trial but failed to maintain LDL-C ≤100 over the 1-year follow-up period.

	Focused Care (n=50)		Control (n=34)	
Lowest LDL	# (%)	Dose (mg)*	# (%)	Dose (mg)*
≤100 mg/dl	33 (67)*	15.6	13 (43)	14.6
<105 mg/dl	36 (73)*	15.7	13 (43)	14.6
<110 mg/dl	37 (76)*	15.8	16 (53)	15.0
At 1-year				
≤100 mg/dl	17 (34)	16.4	8 (24)	11.5
<105 mg/dl	23 (46)*	15.0	8 (24)	11.5
<110 mg/dl	29 (58)*	14.3	8 (24)	11.5

p<0.05 focused care vs control group; *dose recorded as simvastatin equivalent

While patients in the FC group reached target more often than those receiving usual care, maintaining LDL-C levels ≤100 mg/dl continues to present a key treatment challenge.

47. Under use of spironolactone in patients with severe heart failure. *Jennifer M. Sickels, Pharm.D., BCPS,* Michael J. Gonyeau, Pharm.D., Sherri L.

Alexander, Pharm.D., BCPS, Margarita V. Desyatnik, Pharm.D.; Northeastern University, Boston, MA.

PURPOSE: Scientific literature indicates that the use of spironolactone in addition to standard therapy reduces morbidity and mortality in patients with severe heart failure. The purpose of this study was to evaluate the use of spironolactone in class III and IV heart failure patients in four urban teaching hospitals.
METHODS: We conducted a medical record review of all patients with documented systolic heart failure admitted to a general medicine service over a 5-week period. Data retrieved included patient demographics, heart failure class, ejection fraction, spironolactone contraindications, spironolactone use, dose, and frequency, and other heart failure medication use, dose, and frequency. All data reflected patients' baseline status.
RESULTS: A total of 163 patients were included. Our patient population was 80.4% Caucasian, 60.7% male, with a mean age of 70 years (35-99). One hundred seventeen patients had class III or IV heart failure (71.8%). Of these, 14 (12%) were appropriately prescribed spironolactone. Patients admitted with a CHF exacerbation were not more likely to receive spironolactone therapy. Contraindications to spironolactone were identified in 26 patients (25.2%) not prescribed the drug. We identified 77 patients (65.8%) with class III or IV heart failure that were candidates for spironolactone.
CONCLUSION: Two years after publication of the Randomized Aldactone Evaluation Study (RALES), spironolactone is underutilized in the treatment of heart failure. Results of this study indicated that the majority of patients in class III or IV heart failure were not prescribed spironolactone. Improvements in spironolactone prescribing are needed.

48. Cholesterol management in high-risk veterans: comparison of primary providers. *Kathy J. Rinehart, Pharm.D.,* Douglas R. Geraets, Pharm.D., Julie Lehn, Pharm.D., Nelson Lu, M.S.; Veterans Administration Medical Center, Iowa City, IA; Veterans Administration Medical Center, Phoenix, AZ; University of Iowa, Iowa City, IA.

PURPOSE: Treatment of hyperlipidemia reduces cardiovascular events and death in patients with coronary heart disease. This retrospective cohort study compared performance of reaching LDL-lowering goals of primary care providers at a VA Medical Center.
METHODS: Patients with atherosclerotic disease were identified by computer. Fifty patients followed ≥ one year and seen at least twice between June 1, 1997 and May 31, 1999 were randomly selected from four primary care provider groups: medical residents (MR), nurse practitioners and physician assistants (NP/PA), satellite clinic physicians (SCP), and cardiology clinic (CC). Patients with terminal illness, enrolled in Lipid Clinic or clinical pharmacist involvement were excluded. Lipid profiles and drug treatments were compared.
RESULTS: Patients reaching LDL goal, < 100 mg/dl, was low and did not differ by group: MR (39%), NP/PA (31%), SCP (25%) and CC (31%; NS, Fisher's exact test). For patients not at goal, percent of providers not addressing drug therapy at the last visit was highest for SCP (100%) versus MR (78%, $p<0.0031$) and CC (79%, $p<0.0004$). SCP (31%, $p<0.047$) and CC (31%, $p<0.003$) had a significantly higher percentage of patients with LDL ≥ 130 mg/dl, compared to MR (12%). A greater percentage of SCP patients with LDL ≥ 130 mg/dl received a cholesterol-lowering drug compared to CC (53% vs 21%, respectively, $p<0.033$).
CONCLUSION: Attainment of cholesterol goals for secondary prevention of cardiovascular disease was suboptimal and not different amongst providers. A high percentage of all providers did not respond to lipid test results. SCP were more likely to maintain current regimens and not maximize therapy, whereas, CC was less likely to utilize drug treatment.

49. The effect of clonidine on norepinephrine spillover in the isolated rat heart. *Shilpa K. Shah, Pharm.D.,* Kedar Oak, MBBS, Subbu Apparsundaram, Ph.D., Wendell S. Akers, Pharm.D., Ph.D., BCPS; University of Kentucky, Lexington, KY.

PURPOSE: Cardiac norepinephrine (NE) spillover is associated with increased morbidity and mortality in heart failure. Therefore, novel drug therapies directed at suppressing NE release from cardiac sympathetic nerve terminals may provide a new therapeutic approach in the treatment of heart failure. Clonidine is a centrally acting α_2-agonist that reduces sympathetic outflow but its peripheral effects on NE spillover are not well characterized. The purpose of this study is to examine the effects of presynaptic α_2-adrenergic receptor stimulation with clonidine on cardiac NE spillover in the isolated rat heart.
METHODS: Rat hearts with attached sympathetic ganglia were perfused by retrograde coronary artery perfusion with oxygenated Krebs-Hensleit Buffer and maintained at 38°C. A fluid-filled latex balloon connected to an in-line pressure transducer was inserted into the left ventricle for the determination of cardiac function. To determine the effect of clonidine on heart rate and NE spillover, the sympathetic ganglia of each heart was electrically stimulated (2 Hz, 10 V, 60 pulses) before (S1) and after the administration of clonidine or vehicle (S2). Perfusate exiting the heart was collected on ice in one-minute intervals for 5 minutes during each stimulation period for the determination of NE spillover. Norepinephrine was quantified by HPLC with electrochemical detection.
CONCLUSIONS: No between group differences in baseline coronary perfusion pressure or cardiac function parameters were demonstrated between hearts randomized to vehicle (n=3) or clonidine (n=3) treatment. However, preliminary results demonstrate a 53% reduction ($p<0.05$) in cardiac NE spillover from hearts treated with clonidine versus vehicle (S2:S1 ratio: 0.48 and 1.03, respectively).

50. Retrospective evaluation: time to achieve LDL goal in patients with concurrent coronary artery disease and diabetes mellitus. *Alicia D. Kramer, Pharm.D.,* Carrie Johnson, Pharm.D.; University of Cincinnati; Group Health Associates, Cincinnati, OH.

PURPOSE: Coronary heart disease (CHD) is the leading cause of death in the U.S. Persons with type 2 diabetes mellitus (DM) have a 2-4 fold increased risk of developing CHD. Guidelines for the management of hyperlipidemia in patients with existing heart disease recommend < 100 mg/dl as the desirable LDL level. No recommended time frame for the attainment of this desired level is currently available.
This study examines cholesterol screening and management by primary care physicians in order to determine how many patients reach the desired LDL goal and the time it takes to achieve this goal. It will also determine if there is a need for pharmacist assistance in lipid management of these patients.
METHODS: A total of 305 patients from a multi-center physician-owned practice were identified as having coronary artery disease (CAD) and DM. A retrospective chart review was conducted for 170 of these patients to determine the time to reach goal LDL.
RESULTS: Of 170 patients, 125 (73.5%) reached LDL goal at some point during the analysis period. It took these patients an average 33.6 months to reach LDL goal. Forty-five (26.5%) patients never reached goal. One hundred-eleven (79.3%) of the 140 (82.3%) patients on lipid-lowering therapy reached goal.
CONCLUSIONS: Patients at highest risk for coronary events are either not meeting goal LDL levels or are not doing so in a timely fashion due to sub optimal management. The results of this study support implementation of pharmacist intervention. The results also support more aggressive lipid management.

51. Diabetic patients benefit from aggressive heart failure treatment. *Susan J. Morikawa, Pharm.D.,* Donna J. Mateski, M.S., John S. Golden, M.D., Catherine C. Fallick, M.D., Sharon R. Josephson, CRNP, Mary C. Langford, ACNP, Pamela Barnett, R.N.; Kaiser Permanente Mid Atlantic States, Fairfax, VA.

PURPOSE: Optimal pharmacotherapy in congestive heart failure (CHF) has been rapidly evolving. Unfortunately, diabetics are underrepresented in many CHF trials. We sought to assess the role of aggressive CHF treatment in diabetic patients.
METHODS: We analyzed outcomes in 257 consecutive patients referred to our Heart Failure Treatment Program with LVEF <40% and NYHA functional class II-IV heart failure. Of these, 99 (39%) were diabetic (DM) and 158 (61%) were non-diabetic (non-DM). Mean LVEF (25%), baseline renal function, and incidence of CAD were similar; only baseline NYHA functional class differed significantly (2.81 DM vs 2.45 non-DM, $p=0.003$). Following program enrollment, vasodilator, diuretic, β-blocker and spironolactone therapy were initiated or titrated as clinically indicated.
RESULTS: Patients were followed for a mean of 21 months. The use of either ACEIs or ARBs was 100% in each group. Beta-blocker use was 87% in the DM patients and 85% in the non-DM patients (p=NS). Spironolactone was used more commonly in the DM (57%) vs non-DM (42%) patients, ($p=0.02$). NYHA functional class improvement was similar: +0.28 DM vs +0.36 non-DM (p=NS). Hospital days (6 months post-enrollment vs 6 months pre-enrollment) decreased by 35% in the DM patients and by 23% in the non-DM patients (p=NS). Survival at most recent follow-up was similar: 87% DM vs 89% non-DM (p=NS).
CONCLUSIONS: CHF therapy is well tolerated in heart failure patients with diabetes. Diabetic and non-diabetic patients benefit equally from aggressive treatment in a comprehensive, interdisciplinary heart failure management program.

52. A review of clopidogrel usage in Singapore General Hospital. *Ching Hui Lim, B.Sc. (Pharm),* Angelin Lee, B.Sc. (Pharm); Singapore General Hospital, Republic of Singapore.

PURPOSE: Clopidogrel is an antiplatelet agent of which usage greatly increased in Singapore General Hospital. A retrospective study was carried out to determine the pattern of use and adverse events (AEs) in patients prescribed clopidogrel.
METHODS: All hospitalized patients initiated on clopidogrel during September and October 1999 were recruited into the study. Information obtained included indication (s) for antiplatelet therapy, reason (s) for choice of clopidogrel, monitoring parameters (complete blood counts [CBC] and liver function test [LFT]), and AEs.
RESULTS: Of the 166 patients reviewed, 123 (74.1%) were prescribed clopidogrel for prevention of in-stent restenosis after percutaneous

transluminal coronary angioplasty with stenting. Other indications included peripheral artery disease (1.8%), prevention of myocardial infarction (14.5%) or stroke (1.2%), and reduction of recurrent ischemic events in patients with unstable angina (1.8%). Baseline CBC and LFT were obtained in 139 (83.7%) and 47 (28.3%) patients respectively. AEs including chest pain, abdominal pain, diarrhea, and rash were observed in 18 patients, while 3 patients experienced elevated liver enzymes. Clopidogrel was later discontinued in 4 patients due to rash (2), bleeding (1), and general body ache (1).
CONCLUSION: Clopidogrel is mainly used for prophylaxis of restenosis in post-stent patients. AEs noted were mostly gastrointestinal. Baseline monitoring is recommended before initiation of clopidogrel; post-initiation monitoring should be carried out at the physician's discretion. A set of guidelines was developed based on this study, with input from consultant neurologists and cardiologists. These guidelines will be used to increase physicians' awareness of appropriate clopidogrel usage and monitoring.

53. Evaluating congestive heart failure management: optimizing treatment in an outpatient setting. *Stuti Sinha, Pharm.D.,* Michael B. Doherty, Jr., Pharm.D.; University of Maryland, Baltimore, MD; University of Cincinnati, Cincinnati, OH.

PURPOSE: The purpose of this study was to assess the current prescribing patterns for CHF, and enhance compliance with guideline recommendations, in five clinics that provide care to an indigent patient population.
METHODS: Patients who had physician visits for CHF (ICD-9 code 428.0) between July 1, 1999 and June 30, 2000 were identified through the computerized database of the Cincinnati Health Department. A retrospective chart review of 54 CHF patients was conducted in two phases. Physicians were provided with an in-service with results from phase-1 (baseline) and an update on CHF management. Phase-2 was conducted 6 months after the in-service to evaluate its impact.
RESULTS: Fifty-four patient charts were reviewed. There was an increase from baseline in the utilization of ACE-Is by 3.7% to 59.3%, ARBs by 9.3% to 16.7%, BBs by 1.8% to 33.3%, and spironolactone by 13.0% to 20.4%. The percentage of patients on optimal doses of ACE-Is and BBs increased by 3.7% to 11.1%. Similarly, the percentage of patients on neither an ACE-I nor a BB decreased by 3.7% to 24.1%. The use of combination of hydralazine and ISDN and diuretics remained unchanged. There was also a decrease in the use of NSAIDs by 3.7%, but an increase in the use of COX-2 inhibitors and metformin by 11.1% and 5.6%, respectively.
CONCLUSIONS: Overall, we found that indigent patients with CHF in large urban city clinics were receiving appropriate management of their CHF. In addition, the impact of a CHF in-service further enhanced compliance with CHF guidelines. However, there is scope for improvement with increased utilization of first line agents, greater achievement of recommended doses, and removal of deleterious agents.

54. Patients taking fewer prescription medications are less adherent with chronic cardiovascular medication regimens. *Stephen J. Shalansky, Pharm.D.,* Adrian R. Levy, Ph.D., Richard Wanbon, B.Sc.Pharm., Gabriel Loh, B.Sc.Pharm., Roohina Virk, B.Sc.Pharm., Lisa Lui, B.Sc.Pharm.; St. Paul's Hospital, Vancouver, BC, Canada; University of British Columbia, Vancouver, BC, Canada.

PURPOSE: It is generally assumed that increasing regimen complexity results in lower medication adherence, but there is little empirical evidence. The goal of this study was to determine the relationship between the number of medications consumed and adherence with chronic cardiovascular regimens.
METHODS: A survey was administered to 367 patients who had taken an angiotensin converting enzyme inhibitor or lipid lowering medication for at least 3 consecutive months. Information was collected on non-prescription drug use, reported adherence, adverse effects, and use of adherence aids. Prescription drug use data over the previous 12 months was obtained for each patient from the British Columbia prescription database. Adherence for each prescription medication was calculated based on prescription fill dates and number of days supplied. Univariate and multivariate analyses were used to identify predictors of non-adherence (<80%) with cardiovascular medications.
RESULTS: Forty-five (14%) patients were categorized as non-adherent. Non-adherent patients took fewer regularly scheduled prescription medications per day (4.1 ± 2.7 vs 5.9 ± 3.4, p<0.001), fewer doses per day (6.0 ± 4.7 vs 8.6 ± 5.7, p=0.005), and had fewer administration times per day (1.8 ± 0.7 vs 2.4 ± 0.9, p=0.001). A multivariate logistic regression model adjusting for age, gender, reported adverse effects, reported non-prescription drug use, and use of adherence aids identified fewer regularly scheduled prescription drugs was an independent predictor of non-adherence with chronic cardiovascular medications (OR 0.84 per medication, 95% CI 0.74 – 0.94, p=0.004).
CONCLUSIONS: Contrary to popular belief, taking fewer medications is associated with lower adherence with chronic cardiovascular regimens.

Critical Care

55. The incidence of heparin-induced thrombocytopenia in a community hospital ICU/CCU. Arun K. Verma, M.Sc.Pharm., *Stephen J. Shalansky, Pharm.D.*, Marc Levine, Ph.D., Cedric J. Carter, M.B., FCCP, John G. Kelton, MD; University of British Columbia, Vancouver, BC, Canada; St. Paul's Hospital, Vancouver, BC, Canada; Children's & Women's Health Centre of British Columbia, Vancouver, BC, Canada; Vancouver Hospital & Health Sciences Centre, Vancouver, BC, Canada; McMaster University, Hamilton, ON, Canada.

PURPOSE: Heparin-induced thrombocytopenia (HIT) occurs in 1 - 3% of post-operative surgical patients, but is difficult to diagnose as there are no uniform clinical and diagnostic criteria. This study estimated the incidence of heparin-induced thrombocytopenia (HIT) in community hospital ICU/CCU patients based on clinical criteria and results from two diagnostic tests: the enzyme – linked immunosorbant assay (ELISA) and the ^{14}C-serotonin release assay (SRA).
METHODS: Data were collected for 748 consecutive heparin-treated ICU/CCU patients. HIT was diagnosed as follows: (a) two or more consecutive platelet counts < 150 x 10^9/L or > 33% decrease in platelet count after 4 days of heparin therapy, or any time after initiating heparin for patients exposed to heparin within the previous 8 weeks, and (b) positive results from both assays.
RESULTS: Forty patients (5.3%; 95% CI, 3.7% - 6.9%) met the clinical criteria for HIT, one of whom (ICU patient) had positive results from both assays, yielding a HIT incidence of 0.14% (95% CI, 0.003% to 0.75%). The results from diagnostic testing for 3 groups of patients were:

Patient Groups	Clinical Presentation	Serum Available	ELISA Positive	SRA Positive	ELISA and SRA Positive
Controls (n)[a]	96	90	14	3	2
Early Tcp (n)[b]	82	60	4	0	0
HIT (n)	40	32	10	1	1

[a] received heparin for 5 or more days, but did not develop thrombocytopenia (tcp); [b] thrombocytopenia within 4 days of starting heparin, no heparin exposure within the previous 8 weeks

CONCLUSION: The apparent incidence of HIT (<1%) is lower in this population than that reported in surgical patients. The ELISA is less specific than the SRA, and the false positive rate for the 2 assays combined may complicate diagnosis of HIT in ICU/CCU patients.

56. The effects of pre-operative low molecular weight heparin (enoxaparin) versus unfractionated heparin on bleeding in coronary artery bypass graft patients. *Michelle L. Monroe, Pharm.D.,* Neal D. Kon, M.D., Wesley G. Byerly, Pharm.D., Marc G. Reichert, Pharm.D.; Wake Forest University Baptist Medical Center; Wake Forest University, Winston-Salem, NC.

PURPOSE: Low-molecular-weight heparins (LMWHs) have increasingly replaced unfractionated heparin (UFH) in acute coronary syndrome (ACS). The prolonged half-life of LMWHs may lead to increased bleeding complications in patients who require coronary artery bypass graft (CABG) intervention. This study compared the frequency of bleeding complications between CABG patients who received pre-operative enoxaparin versus pre-operative UFH for ACS.
METHODS: A retrospective chart review of 198 (99 per group) first-time, elective CABG patients was conducted. Baseline hematologic characteristics, pre-operative anti-coagulant/anti-platelet medications, CABG procedure information, and the volume of blood products transfused intra-operatively and within 24 hours post-bypass were collected.
RESULTS: Seventy-four enoxaparin patients and 69 UFH patients were included in the study. The enoxaparin group received an average of 130.8 ± 182.6 ml of platelets per patient compared to 70.3 ± 147.6 ml in the UFH group (p=0.024). An average of 689.2 ± 731.9 ml versus 472.8 ± 625.7 ml of red blood cells per patient was utilized in the enoxaparin and UFH groups, respectively (p=0.058). Enoxaparin patients received 83.8 ± 234.1 ml of fresh frozen plasma versus 37.7 ± 172.4 ml in the UFH group (p=0.12). Enoxaparin patients required significantly more aminocaproic acid than UFH patients (25.1 ± 8.4 vs 19.2 ± 6.1 g; p<0.01). No transfusions were required in 47.9% of UFH patients compared to 32.4% of enoxaparin patients. Moderate to severe bleeding occurred in 24.6% of UFH patients compared to 41.9% of enoxaparin patients.
CONCLUSION: Enoxaparin patients required more blood products and experienced more severe bleeding than UFH patients. Based on these results, consideration should be given to converting enoxaparin to UFH before a CABG procedure.

57. Comparison of a glycemic control protocol versus sliding scale insulin in the management of type II diabetics in the medical intensive care unit. *John Marshall, Pharm.D., BCPS,* Ronald J. DeBellis, Pharm.D., Richard S. Irwin, M.D., Michael Thompson, M.D.; Massachusetts College of Pharmacy and Health Sciences, Boston, MA; University of Massachusetts Memorial Medical Center, Worcester, MA.

PURPOSE: We evaluated the effectiveness of a glycemic control protocol versus sliding scale insulin in managing type II diabetics in the Medical Intensive Care Unit (MICU).(consider removing the hospital name-abstracts are reviewed anonymously and by giving the location you take away that advantage).

METHODS: 10 Type II diabetics admitted to the MICU with hyperglycemia (Blood Glucose greater than 250 mg/dl) were placed on a glycemic control protocol. The foundation of the protocol was an insulin drip algorithm followed by conversion to a scheduled glycemic control regimen. The intervention group was compared to 12 patients with similar demographics and type II diabetes who were placed on a MD prescribed sliding scale insulin regimen while in the MICU. Episode rates were calculated for each patient. An episode was defined as any capillary blood glucose measurement outside the acceptable range (60-250 mg/dl). Unpaired t-tests were used to compare the groups.
RESULTS: A total of 22 patients were enrolled (10 protocol, 12 control). Mean capillary blood glucose was 217 mg/dl ± 57 in the protocol group compared to 248 mg/dl ± 73 in the control group ($p<0.00005$). The total number of episodes in the protocol and control groups was 207 and 419 respectively. Patients in the protocol group had an average episode rate of 0.209, while those in the control group had an average episode rate of 0.450 ($p<0.004$).
CONCLUSION: We demonstrated that the use of a glycemic control protocol is superior to sliding scale insulin in controlling blood glucose in type II diabetics while in the MICU.

58. An evaluation of fluconazole loading doses and duration of therapy in the treatment of candiduria. Ayanna Philips, Pharm.D., *Roopali Sharma, Pharm.D.*; Long Island University, Brooklyn, NY.

BACKGROUND: Loading doses of fluconazole are used to treat candiduria; however, the role of fluconazole loading doses in the management of candiduria has not been established.
PURPOSE: An investigation was conducted to evaluate the effect of fluconazole loading doses on the microbiological and clinical outcomes of patients who were treated for candiduria. An assessment of microbiologic and clinical outcomes in relation to the duration of fluconazole treatment was also determined.
METHODS: Microbiology records were screened to identify patients with candiduria, defined as $\geq 10^3$ colony forming units/ml of candida in at least one urine culture, between October 1, 1999 and September 30, 2000. Pharmacy records were also reviewed. The medical records of the patients included in the study were reviewed to obtain demographics, microbiologic data, clinical data and duration of therapy.
RESULTS: Forty patients met the inclusion criteria. These patients were divided into two groups: group A (n=18) consisted of patients who received loading doses (LD), group B, (n=22) patients who did not receive LD. There were no significant difference in microbiologic cure rates between group A (66.7%) and group B (63.6%; $p>0.05$). Clinical cure was evaluated in 35 patients and the cure rate in group A and group B was 50% and 35.3% respectively. ($p>0.05$). There was no statistically significant difference in clinical and microbiological cure rates relative to duration of fluconazole therapy ($p>0.05$).
CONCLUSION: The results of this study indicate that neither the use of fluconazole loading doses, nor duration of treatment influences microbiologic or clinical outcomes in the management of candiduria.

59. A survey of medical institutions on deep venous thrombosis prophylaxis in patients following cardiothoracic surgery. *Marc G. Reichert, Pharm.D.,* Sanjay Gujrati, Pharm.D.; Wake Forest University; Baptist Medical Center, Winston-Salem, NC.

PURPOSE: This survey was conducted to determine current practice in the prophylaxis of deep venous thrombosis (DVT) in cardiothoracic surgery (CTS) in the absence of published guidelines.
METHODS: A 16-question survey was sent to pharmacy departments of 57 hospitals with well-recognized CTS programs.
RESULTS: Twenty-eight of the 57 centers returned the survey (49%). The most frequently cited characteristics of the respondent and institution were clinical pharmacists (42.9%), overseeing clinical services (35.7%), from large (>500 beds) teaching hospitals (85%). The majority of centers had 11-20 CTS ICU beds and >20 CTS floor beds. None of the respondent's institutions monitor the frequency of DVT in the CTS population. Eighty-two percent of responding institutions utilize prophylaxis for those at risk, and 11% use prophylaxis routinely. The majority of institutions (60.7%) used variable prophylaxis methods with either low-dose unfractionated heparin (LDUH) or graduated compression stockings (GCS) making up the largest percentage of this group (21.4%). In patients at risk for bleeding, GCS (35.7%) and GCS or intermittent pneumatic compression (IPC; 35.7%) were most frequently cited. The method of prophylaxis was chosen based on risk factors and physician preference most frequently (32.1%). The risk factors consistently chosen for considering DVT prophylaxis included immobility (100%), hypercoagulable state (88%), history of DVT (100%) and obesity (96%).
CONCLUSION: A large variety of DVT prophylaxis methodologies are being used in the CTS population. Additionally, inconsistency existed in regard to several risk factors. A randomized, double-blind study is needed in this patient population.

60. Risk factors and clinical outcomes for *Stenotrophomonas maltophilia* nosocomial pneumonia. *Scott D. Hanes, Pharm.D.,* Elizabeth A. Tolley, Ph.D., Kutay Demirkan, Pharm.D., G. Christopher Wood, Pharm.D., Martin A. Croce, M.D., Bradley A. Boucher, Pharm.D.; University of Tennessee Health Science Center; Baptist Memorial Hospital, Memphis, TN.

PURPOSE: Inappropriate empiric antibiotic therapy is associated with increased morbidity and mortality in patients with nosocomial pneumonia (NP). *Stenotrophomonas maltophilia* is an increasingly important nosocomial pathogen; however most empiric antibiotic regimens do not provide adequate activity against this gram-negative bacterium. Knowledge of the risk factors associated *with S. maltophilia* NP may better guide empiric antibiotic therapy selection.
METHODS: Potential risk factors for *S. maltophilia* NP were retrospectively analyzed in 163 critically ill trauma patients with a single late-onset (≥ 7 days) gram-negative bacteria NP episode (n=130) and multiple late-onset gram-negative bacteria NP episodes (n=33) using multivariate analysis. Clinical outcomes were also assessed.
RESULTS: *S. maltophilia* occurred in 14% and 24% of patients with single and multiple NP episodes, respectively. Cefepime exposure (OR 3.31, 95% CI 1.12-9.72) and tracheostomy (OR 5.37, 95% CI 1.14-25.15) were identified as risk factors associated with single episode *S. maltophilia* NP. For multiple episode NP patients, injury severity score (OR 1.14, 95% CI 1.03-1.27) and pulmonary contusion (OR 14.69, 1.16-185.07) were identified as risk factors for *S. maltophilia.* Mortality rates were similar between NP episodes caused by *S. maltophilia* compared to other gram-negative bacteria (23.1% vs 17.5%, p=0.69). In survivors, *S. maltophilia* NP was associated with longer ICU stay (38.5 vs 24 days, p=0.011), longer hospital stay (49 vs 37 days, p=0.013), and prolonged mechanical ventilation (35.5 vs 19 days, p=0.006) compared to NP caused by other gram-negative bacteria.
CONCLUSIONS: Risk factors for *S. maltophilia* NP are associated with selected treatment modalities in patients with single NP episodes. The type and severity of injury have a greater influence in patients with multiple NP episodes. These risk factors should be considered when selecting empiric antibiotic therapy for NP in trauma patients in an attempt to improve patient outcomes.

61. Dipeptide transport following thermal injury. *Jeffrey P. Gonzales, Pharm.D.,* David R. Foster, Pharm.D., Lynda S. Welage, Pharm.D., FCCP; University of Michigan, Ann Arbor, MI.

PURPOSE: The integrity of the intestinal barrier is diminished following thermal injury; the absorption of large hydrophilic macromolecules (via paracellular transport) is often enhanced, whereas the absorption of amino acids may be impaired. Although the use of peptides as a source of protein has gained considerable attention, limited data exists regarding the impact of thermal injury on peptide transport. This study was designed to evaluate the impact of thermal injury on oligopeptide transport, using the dipeptide glycylsarcosine (Gly-Sar) as a marker substrate.
METHODS: Male Sprague Dawley rats were assigned to burn (n=7) or sham (n=8) groups. Rats in the burn group were anesthetized and received a 30% body surface area, full thickness scald burn. Twenty-four hours following burn/sham treatment, rats were anesthetized, underwent laparotomy and the proximal jejunum was cannulated. The jejunal segment was perfused with isotonic buffer containing 0.5 mM [C^{14}] Gly-Sar, and intestinal permeability was calculated.
RESULTS: The effective intestinal permeability (Peff) of [C^{14}] Gly-Sar was similar in burn and sham rats [$6.67 \pm 2.27 \times 10^{-5}$ vs $7.58 \pm 2.20 \times 10^{-5}$ cm/sec, respectively] ($p=0.45$). Intestinal wall permeability (Pw) was $1.84 \pm 1.58 \times 10^{-4}$ cm/sec in burn rats, and $2.29 \pm 1.67 \times 10^{-4}$ cm/sec in sham rats ($p=0.60$). Fraction of [C^{14}] Gly-Sar dose absorbed approached 100% in both groups, and did not differ between burn and sham rats (95.0% vs 96.8%, respectively; $p=0.38$).
CONCLUSIONS: Intestinal transport of the dipeptide marker Gly-Sar is preserved 24 hours following thermal injury in rats. This offers further support for the use of peptides as a source of protein in critically ill patients.

62. Efficacy of metoclopramide in exploratory laparotomy patients. *Maria L. Seta, Pharm.D.,* Pramodini B. Kale-Pradhan, Pharm.D.; Wayne State University; St. John Hospital and Medical Center, Detroit, MI.

PURPOSE: To assess the efficacy of Metoclopramide for the treatment of postoperative ileus in exploratory laparotomy patients.
METHODS: This is a prospective observational study of surgical intensive care unit (SICU) patients who underwent exploratory laparotomy. Neurosurgery patients or patients with a history of obstructive gastrointestinal disease were excluded. The primary endpoint is time to the first postoperative BM. Secondary endpoints include length of stay in the SICU and total hospital length of stay (LOS). Patient specific factors such as APACHE II scores, number of days to tolerate an oral diet and narcotic use are included in data analysis.
RESULTS: 16 received Metoclopramide 10 mg IV beginning on the day of surgery and continued on 10 mg every 6 hours; and 16 were control patients. There were no significant differences in demographics. The mean number of days to the first BM was nearly identical in both groups. The total and average amounts of opioid narcotics measured in morphine sulfate (MS) equivalents, LOS in SICU and total LOS were not significant between groups.

	Metoclopramide	Control	P value
n	16	16	-
Age (years)	56.8	67.5	0.148
Gender (M/F)	8/8	7/9	1.00
APACHE II	14	15.3	0.54
Days to First BM	4.8	4.7	0.93
Tolerance to Oral Feeding	5.7	4.8	0.48
MS (mg/day)	18	20.1	0.63
Total Narcotic use (MS equivalents)	126.1	157.2	0.66
LOS Days (SICU/Total)	8.3/18	8.6/20.1	0.89/0.63

CONCLUSION: The time to first BM was not significantly different between the groups. Metoclopramide did not decrease the LOS. Continuation of metoclopramide after BM is unnecessary. There is a need to develop practice guidelines.

Drug Delivery

63. Bioavailability and pharmacokinetics of intranasal hydromorphone in treated and untreated allergic rhinitis patients. Patrick J. McNamara, Ph.D., George A. Davis, Pharm.D., *Jodi L. Miller, Pharm.D.,* Anita C. Rudy, Ph.D., Daniel P. Wermeling, Pharm.D.; University of Kentucky, Lexington, KY.

PURPOSE: To compare the bioavailability and pharmacokinetics (PK) in treated vs untreated allergic rhinitis patients following intranasal (IN) hydromorphone (HM) administration.
METHODS: Twelve patients participated in this IRB-approved, randomized, crossover study. The treatments, each separated by one week, consisted of 2 mg HM IV, 2 mg HM IN without allergy treatment for 6 days (IN-untreated), and 2 mg HM IN after 6 days of IN fluticasone (IN-treated). Blood samples were collected serially 0-16 h. Plasma concentrations were determined by LC/MS/MS. PK parameters were determined using noncompartmental methods. An ANOVA model was used for statistical analysis.
RESULTS: Mean (%CV) are given except for T_{max}, where median (range) is given.

Parameter	IV	IN-untreated	IN-treated
T_{max} (h)	0.167 (0.083-0.167)	0.25 (0.167-0.5)	0.5 (0.167-1.967)
C_{max} (pg/ml)	34762 (47.0)	3563 (36.3)	3024 (57.3)
$t_{1/2}$ (h)	9.01 (42.4)	8.52 (34.1)	6.11 (50.0)
AUC_{0-t} (pg•h/ml)	15539 (20.7)	6698 (28.9)	7755 (29.6)
$AUC_{0-\infty}$ (pg•h/ml)	16819 (20.2)	7698 (26.5)	8474 (25.8)
CL/F or CL_{ss}/F (L/h)	109 (20.0)	247 (28.2)	227 (36.2)
F (%)	-	46.9 (29.8)	51.2 (27.1)

No significant adverse events or nasal pathology was observed. Carryover effects were insignificant ($p>0.1$). Using rank-transformed T_{max}, there was a significant difference between IN treatments ($p=0.02$). No statistical AUC and C_{max} differences were detected.
CONCLUSION: Based on these results, a slower onset of action would be expected clinically for fluticasone-treated rhinitis patients. Future studies are warranted to allow direct PK comparison with healthy subjects and to further determine how pain management strategies may be impacted using IN HM in this patient population.

Education

64. Using study guides to promote active learning in an advanced pharmacotherapeutics course. *Sharon See, Pharm.D.,* Tina Kanmaz, Pharm.D., Judith Beizer, Pharm.D., Gladys El-Chaar, Pharm.D., Laura Gianni, Pharm.D., Andrew Skirvin, Pharm.D., Michael Torre, M.S.; St. John's University, Jamaica, NY.

PURPOSE: A Pharm.D. lecture-based advanced pharmacotherapeutics course was revised using an active learning, case-based approach. We suggest that the use of study guides outside of class and devoting class time for pharmaceutical care plan (PCP) preparation and discussion, will enhance students' ability to think critically, write a PCP, and collaborate with others.
METHODS: Study guides were prepared and distributed for each topic. Students were responsible for completing the study guide using assigned readings prior to class. The two-hour class was divided into three periods. The study guide was discussed during the first period. During the second period, pre-assigned student groups were given a patient case and asked to prepare a PCP. The last period was allocated for group presentations and discussion. A survey was distributed at the end of the semester to assess student satisfaction with this new method.
RESULTS: Forty-six students completed the survey. Students strongly agreed/agreed that the new format increased their ability to think critically (67%) and their competency in PCP preparation (78%). Students also strongly agreed/agreed that the study guides were useful (70%), the group discussions enhanced group collaboration (59%), and the required readings enhanced learning (87%). Despite the positive feedback, students requested more didactic lecturing and time for PCP preparation.
CONCLUSION: This innovative teaching approach was beneficial to students in many aspects. The results illustrate student acceptance of active learning techniques as compared to a passive lecture-based format and raise the possibility of using this method in other courses.

65. Rankings of U.S. pharmacy schools based on perception, funding, and publications. *Dennis F. Thompson, Pharm.D., FCCP,* Randall P. Sharp, Pharm.D.; Southwestern Oklahoma State University, Weatherford, OK.

PURPOSE: To provide a relative ranking of U.S. pharmacy schools based on the three criteria of perception, funding, and publications
METHODS: Perception rankings were obtained from the 1997 report of pharmacy school rankings from *U.S. News*. Funding was determined by obtaining National Institutes of Health funding of pharmacy schools from their web site. Average yearly funding was calculated for each school over a 20-year time period (1981-2000). Publication rankings were determined by our previous work with calculating publication rates from the Geographic Index of *Science Citation Index*. Average yearly publications per school were determined over a 22-year time period (1976-1997) and averaged per year. These three rankings were then combined to create an overall score for each pharmacy school.
RESULTS: The University of California at San Francisco (UCSF) was the top pharmacy school using these criteria. UCSF also led all schools in the three individual criteria. Purdue, University of Texas, Ohio State, Michigan, Arizona, Illinois, Kentucky, Minnesota, and Florida round out the top ten schools.
CONCLUSION: These data provide a normative starting place to track trends in the areas of funding, publications, and perceptions of pharmacy schools. The combination of multiple criteria to rank pharmacy schools provides a better overall assessment than any single criteria.

66E. Developing new pharmacy practice faculty. *Cynthia L. Raehl, Pharm.D.,* Arthur A. Nelson Jr., R.Ph., Ph.D.; Texas Tech University Health Sciences Center, Amarillo, TX.

OBJECTIVE: A formal faculty development program targeting 31 assistant professors in their first through fifth years is described.
METHODS: The multiyear program includes 1) school-wide faculty orientation week, 2) first year Chair/Regional Dean faculty member biweekly meetings resulting in an annual prospective faculty development plan and performance evaluation, 3) formal department and school-wide faculty retreats, 4) visiting professor program, 5) third-year mid-probationary internal peer review.
RESULTS: Program refinement continues after five years. Tenure and non-tenure track practice faculty share development needs in teaching and practice. Teaching acclimation first concentrates on course mechanics, team responsibilities and instructional technology; and in later years individual teaching style and assessment techniques. Practice development concentrates on instituting a hierarchical clerkship teaching model incorporating faculty, resident, P3 and P4 students. Documenting clinical and fiscal outcomes for both individual and group practitioners remains a yearly challenge. Chair identified research development needs begin with explicit discussion of tenure requirements, establishing a writing regimen, and preparing written research program statements. Tenure track faculty highest ranked research needs are: funding (1.71 ± 0.49 on a 1-5 scale), research assistants (1.86 ± 0.69) and limited clerkship duties (1.86 ± 0.90). A grantsmanship workshop and internal seed and equipment grant applications generally precede external grant applications.
IMPLICATIONS: New faculty struggle to balance multiple responsibilities and grasp institutional expectations for performance and eventual promotion and/or tenure. A formal faculty development program is critical for newly appointed assistant professors.
Presented at the 2001 Annual Meeting of the American Association of Colleges of Pharmacy, Toronto, Canada, July 10, 2001.

67. Physicians' knowledge of a clinical pharmacist's role in a family medicine residency program. *Nicole S. Culhane, Pharm.D., BCPS*; Wilkes University, Wilkes-Barre, PA.

PURPOSE: A 16-item survey was developed to assess medical residents' knowledge of the role of a clinical pharmacist in three main areas: patient education, patient care, and medical resident education.
METHODS: Sixteen medical residents completed a baseline and follow-up survey (mean 18 months). The survey questions pertained to demographics and previous pharmacist interactions as well as 16 questions using a five-point Likert scale (1 = strongly disagree and 5 = strongly agree). The baseline survey results were compared to an identical follow-up survey to assess any change in resident knowledge after interacting with a clinical pharmacist in the residency program.
RESULTS: The majority of the responses in the pre-test were favorable. Fourteen out of 16 responses had mean scores greater than 4. When comparing baseline with follow-up results, no items were statistically different. However, medical residents without previous interactions with a clinical pharmacist demonstrated the largest positive difference between baseline and follow-up survey responses.

CONCLUSIONS: Incoming medical residents possessed a significant baseline knowledge pertaining to the role of clinical pharmacists. The lack of significant differences between baseline and follow-up results may have been due to either high baseline responses or the small sample size. Further evaluation of incoming medical residents is necessary to specifically determine which areas of pharmacy practice physicians are most knowledgeable and where clinical pharmacists can make the most impact.

68. Assessing attitudinal changes in a didactic women's health course. Megan N. Alvin, Pharm.D., *Keri A. Mattes, Pharm.D.*; St. Louis College of Pharmacy, St. Louis, MO.

PURPOSE: In courses focused on pharmaceutical care, educators often attempt to impart attitudes of openness and awareness of the entire patient to encourage students to consider all factors that will affect patients' health. Influencing students' attitudes can be more difficult than imparting factual knowledge. The purpose of this analysis was to determine if a didactic course in women's health emphasizing social awareness could positively influence students' attitudes. The course required students to participate in a community service activity and reflect upon a patient's social environment by writing short essays on five different women's issues after guest speaker presentations.
METHODS: Over two semesters, questionnaires were administered to a total of 21 students during their first class meeting, and readministered at the end of the course. The questionnaire consisted of 44 items which students answered using a Likert scale ranging from strongly agrees to strongly disagrees. Questions were divided into three categories: opinion, judgment, and fact. Inferences about attitudinal changes were based on favorable responses to the opinion and judgment questions. Paired, one-tailed t-tests were used to evaluate significant changes in response to questions.
RESULTS: Responses for 26 of the 44 questions showed a significant ($p<0.05$) shift to a more favorable response. Of these 26 questions, 24 of them were considered to have an attitudinal component.
CONCLUSIONS: The data indicate that a didactic course focused on a patient's social environment can positively influence students' attitudes.

Endocrinology

69E. Impact of community pharmacists on persons with diabetes. *Rajul M. Gandhi, Pharm.D.,* Jay D. Currie, Pharm.D., Matthew C. Osterhaus, B.S.Pharm., Karen B. Farris, Ph.D.; University of Iowa, Iowa City, IA; Osterhaus Pharmacy, Maquoketa, IA.

PURPOSE: This study was designed to determine whether community pharmacists can 1) identify persons with diabetes (PWD) who have not met the American Diabetes Association (ADA) guidelines for HbA_{1c} testing, annual dilated fundoscopic eye exams (DFE), and pneumococcal vaccinations (PPV); 2) provide PWD education regarding the above markers; and 3) collaborate with physicians and optometrists to improve compliance rates with ADA recommendations.
METHODS: Eligibles included PWD receiving medications and/or diabetic supplies from an independent community pharmacy. Patients were randomized to one of two groups. One group received one-on-one education and pharmacist intervention with physician regarding ADA recommendations. The second group received the same education in a group format without intervention.
RESULTS: Forty patients were randomized. Sixteen patients in the one-on-one education group and 18 in the group session completed the study. Baseline characteristics and adherence rates to ADA guidelines were similar between groups. Pharmacists improved PPV compliance rates for one-on-one patients versus group patients ($p=0.029$). The mean number of HbA_{1c}s increased to meet ADA standards for both groups ($p=0.019$) as did PPVs ($p=0.046$); the overall rate of DFEs showed a trend toward improvement ($p=0.102$). There were no differences between groups for HbA_{1c}s and DFEs. Patient-reported ratings on health and diabetic control were examined. When combining both groups, patient-reported diabetic control improved ($p=0.001$).
CONCLUSION: Pharmacists identified PWD who needed additional care. Overall compliance with ADA guidelines was improved, particularly with PPVs. Pharmacists worked effectively with physicians to improve care of this patient group.
Presented at the Annual Meeting of the American Pharmaceutical Association, San Francisco, CA, March 16-18, 2001.

70. The use of thiazolidinediones in a VA medical center population. *Amie D. McCord, Pharm.D.,* Carla A. Zeilmann, Pharm.D., BCPS, Thomas Meyer, R.Ph., Amy S. Flusche, Pharm.D.; St. Louis College of Pharmacy; Veterans Affairs Medical Center, St. Louis, MO.

PURPOSE: This drug utilization review evaluates the use of thiazolidinediones in a VA population, specifically: 1) the effectiveness of agents in lowering HgbA1c values and 2) the appropriateness of liver function test (LFT) monitoring by prescribers.
METHODS: Medical records of 139 patients receiving thiazolidinediones within the VA medical center were reviewed. Information including demographics, concomitant medications and disease states, HgbA1c values, and frequency of LFT monitoring was collected. This data was collected retrospectively from the time of initiation of therapy through April 2001.
RESULTS: Thiazolidinediones were prescribed to 139 patients and the mean duration of therapy was 7.1 months. The mean reduction in HgbA1c for all treated patients was 0.83%. When comparing rosiglitazone with pioglitazone there were no significant differences in mean change in HgbA1c. There were also no significant differences when comparing change in HgbA1c among different age groups or different races. Only 38% of patients studied underwent LFT monitoring at appropriate intervals and no statistically significant differences were observed when comparing agents, ages, or race.
CONCLUSION: The use of thiazolidinediones produced a significant reduction in HbA1c which was observed with both agents, in patients of all ages, and in both Caucasians and African Americans. The majority of patients did not have LFT monitoring at intervals consistent with published guidelines and this finding was not significantly different among the different demographic groups studied. Although the agents appear to be effective, there is a need for more stringent monitoring in order to ensure patient safety.

71. Retrospective claims database analysis assessing therapy changes of oral hypoglycemic agents in type 2 diabetes. *Amishi B. Shah, Pharm.D.,* Doug Gause, Dr.PH., Jennifer C.Y. Sung, Pharm.D., M.S., Nate S. Freimark, B.S.; Wilkes University, Wilkes-Barre, PA; Novartis Pharmaceutical Corporation, East Hanover, NJ.

PURPOSE: Identify the rate of therapy changes of oral hypoglycemic agent (OHA) therapy among patients with type 2 diabetes in a longitudinal cohort using a retrospective claims database analysis.
METHODS: Data were extracted from a proprietary claims database including patients who receive medical and pharmacy benefits from managed care organizations. We identified continuously enrolled patients in 1998 and 1999 with at least one ICD-9 code for diabetes (250xx) and a prescription for an OHA. Patients were included if they did not take insulin or OHAs in the 3 months prior to the index OHA prescription and were followed through 6 months (n=8134), 12 months (n=5724) and 18 months (n=2367). The primary outcome was therapy change including switching, addition of another OHA and dose titration.
RESULTS: The number of therapy changes to OHA regimens, titrations, and additions increased with length of follow-up. Patients had 1.26 ± 2.07, 2.89 ± 3.94 and 4.95 ± 6.07 therapy changes over 6, 12, and 18 months of follow-up, respectively. Addition of another OHA was the most common one. The mean number of titrations per patient was highest for metformin, followed by repaglinide for all lengths of follow up.
CONCLUSIONS: This study shows that with increasing length of OHA therapy, therapy changes occur more frequently and therefore may have economic implications in the clinical management of diabetes.

Gastroenterology

72E. Rabeprazole efficacy in GERD patients reporting unsatisfactory relief with prior omeprazole or lansoprazole therapy. Malcolm Robinson, M.D., Leonard Jokubaitis, M.D., *Anita Murthy, Pharm.D.*; Oklahoma Foundation for Digestive Research, Oklahoma City, OK; University of Oklahoma, Oklahoma City, OK; Janssen Pharmaceutica Inc., Titusville, NJ; Eisai Inc., Teaneck, NJ.

PURPOSE: The Future of Acid Suppression Therapy (F.A.S.T.) Trial, an open-label study, evaluated the efficacy of rabeprazole (RAB) therapy on symptom severity in 2579 erosive GERD patients. The present analysis involves only patients reporting prior ineffective relief with either omeprazole (OME; n=290) or lansoprazole (LAN; n=212) within 3 months of study entry.
METHODS: Patients received RAB 20 mg once daily for 8 weeks and reported GERD symptoms via an interactive voice response system on Days 1–7 and Day 28, using a 4-point severity scale (0 = none to 3 = severe). 24-hour heartburn symptom assessment was based on the greater severity recorded for either daytime or nighttime, with no imputation for missing data.
RESULTS: RAB significantly decreased mean symptom score from baseline for daytime and nighttime heartburn at all time points assessed for patients previously experiencing ineffective relief using OME ($p\leq0.006$) or LAN ($p\leq0.002$) therapy. The percentages of patients reporting complete relief with RAB were:

Study Day	Prior Therapy	Daytime Heartburn	Nighttime Heartburn	24-Hour Heartburn
Day 7	OME	65.6%	77.3%	63.5%
	LAN	75.5%	76.8%	66.2%
Week 4	OME	82.2%	82.3%	77.2%
	LAN	81.0%	84.4%	74.8%

CONCLUSION: RAB was reported to provide effective relief of daytime and nighttime heartburn symptoms in a majority of patients suffering from erosive GERD who reported ineffective relief with prior OME or LAN therapy.
Published in Gut 2001;48:A25.

73. Cost analysis of the appropriate use of stress ulcer prophylaxis. Pramodini B. Kale-Pradhan, Pharm.D., *Maria L. Seta, Pharm.D.*; Wayne State University; St. John Hospital and Medical Center, Detroit, MI.

PURPOSE: To assess the cost impact of the appropriate use of SUP based on the criteria developed by the American Society of Health System Pharmacists.
METHODS: Data from a previous prospective observational study evaluating the appropriate use of SUP was utilized for cost analysis (CA). Original subject data was reviewed to quantify the total number of doses and route of administration of SUP. The number of intravenous doses received by patients tolerating oral intake was noted. The cost of therapy was based on the wholesale drug cost. CA included the potential for cost savings (CS) by combining the costs of doses given to patients without an indication for SUP, costs incurred by intravenous therapy in patients tolerating oral intake, and cost of using lansoprazole instead of famotidine. Potential CS were annualized from the 2-month data. CS from the 76 patient sample size were extrapolated to total hospital admissions excluding neonates, pediatrics, and obstetrics in the year 2000.
RESULTS:

	SICU	Non-ICU
Gender	21 M, 23 F	17 M, 15 F
Mean Age (years)	62	63
Appropriate SUP	66%	0%
Discharged with SUP	25%	12.9%
Mean Length of SUP therapy (days)	12.6	6.6
Mean Length of Stay	21	7.5

In 15 of 44 (34%) ICU patients SUP was continued upon transfer out of ICU despite absence of risk factors. The patients who were treated for SUP without risk factors received a total of 243 intravenous, 501 oral, and 26 TPN doses of famotidine; 168 doses of sucralfate; and 34 doses of lansoprazole. The combined cost of therapy was $855.44. Fifty-two intravenous doses of famotidine were administered in patients requiring prophylaxis and tolerating PO. This increased the cost of SUP by $109.20. Cost of using lansoprazole instead of famotidine was $27.36. The total avoidable cost was $992 for 2 months. Appropriate use of SUP would save $5952.00 annually for the patients reviewed. Based on 25,596 adult admissions, the annualized CS would be $2,004,570.95.
CONCLUSION: Appropriate use of SUP would generate significant CS.

74. Pharmacokinetic comparison of pantoprazole, omeprazole and esomeprazole. *Robyn G. Karlstadt, M.D.,* Michael S. Burton, Richard B. Lynn, M.D., William Zarycranski, Pharm.D.; Wyeth-Ayerst Laboratories, Philadelphia, PA.

PURPOSE: To assess the pharmacokinetic profiles of single oral doses of three proton pump inhibitors, pantoprazole (P), omeprazole (O), and esomeprazole (E) in healthy volunteers.
METHODS: An open-label, randomized, single oral dose, crossover study with a 72-hour washout period between treatments, used the approved erosive gastroesophageal reflux disease (GERD) dose for each PPI (P 40 mg, O 20 mg, E 20 mg and E 40 mg). Healthy adults (13) were fasted overnight and administered study medication at approximately 8:00 am. They continued to fast for another 6 hours. Blood samples for determination of plasma concentrations were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 18 and 24 hours after dosing. One subject who appeared to be a slow metabolizer was excluded from the analysis. The assays were performed by a validated LC/MS/MS method. Results expressed as mean ± SD.
RESULTS:

	$AUC_{0\text{-inf}}$ (umol-hr/L)	C_{max} (umol/L)	T_{max} (hours)	$t_{1/2}$ (hours)
P	18.0 ± 9.79	8.7 ± 2.57	2.6 ± 0.53	1.2 ± 0.25
O	2.2 ± 1.87	1.0 ± 0.77	2.5 ± 2.53	1.8 ± 1.00
E20	2.8 ± 1.78	1.5 ± 0.63	1.8 ± 0.54	1.0 ± 0.31
E40	7.3 ± 3.80	3.6 ± 0.93	1.8 ± 0.58	1.1 ± 0.31

CONCLUSIONS: This study demonstrates that pantoprazole has the largest AUC and C_{max} after a single, oral, morning dose compared with the approved erosive GERD doses of O, E 20 and E 40. It has been suggested that the greater the drug plasma concentration of a given PPI, the greater the parietal cell concentration and inhibition of acid secretion. The longer a PPI circulates in the bloodstream, the more likely it will bind to pumps activated by multiple meals throughout the day. Pantoprazole's large AUC may explain, in part, the observation in U.S. clinical trials that pantoprazole improves symptoms beginning on day one of therapy and completely eliminates nighttime heartburn by eight weeks in most patients with erosive GERD.

75. Analysis of the effects of α-tocopherol on the diagnostic validity of fecal occult blood testing. *Andrea C. Hall, Pharm.D.,* Anne P. Spencer, Pharm.D., G. Patrick Meier, Ph.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: The purpose of this investigation is to determine if standard doses of vitamin E inhibit the detection of blood using guaiac cards *in vitro* and *in vivo*. Vitamin C is also an antioxidant, and it has a known inhibitory effect on the peroxidase activity necessary to yield a positive guaiac test.
STUDY DESIGN: In-vitro: Multiple solutions containing vitamin E and hemoglobin, vitamin C and hemoglobin, and control solutions, were prepared and tested upon guaiac cards. In-vivo: Fifteen healthy volunteers were enrolled in a prospective, controlled, single-blind, open-label, crossover trial with three phases. After baseline guaiac testing, volunteers consumed red meat and collected sequential stool samples, and then repeated this process with the addition of vitamin E 800 IU daily. Guaiac cards were interpreted in a blinded fashion by trained personnel.
RESULTS: In-vitro: All vitamin E solutions were hemoccult positive at zero and 24 hours. All vitamin C solutions were hemoccult negative. In-vivo: The consumption of vitamin E produced no significant change in the number of volunteers obtaining a positive guaiac result compared to the previous phase (50% vs 35.7%, p>0.05), or the total number of positive guaiac tests (14.3% vs 16.1%, p>0.05), after red meat consumption.
CONCLUSIONS: Vitamin E given in the standard dosage of 800 IU daily does not inhibit the detection of peroxidase activity via the guaiac testing method in-vitro or in-vivo.

76E. Loperamide alters IL-8 secretion in Caco-2 cells via a naloxone reversible process. *Brien L. Neudeck, Pharm.D.,* Jennifer M. Loeb, B.S.; University of Wisconsin, Madison, WI.

PURPOSE: To determine the effect of loperamide on IL-8 secretion in Caco-2 cells.
METHODS: Caco-2 cells (P56-63) were seeded in 24 well plates or 60 mm dishes and grown to confluence. Subtypes of opioid receptors were characterized using RT-PCR. Human recombinant IL-1β was used to stimulate the secretion of IL-8. Cells were treated with serum-free media (control), IL-1β (3 ng/ml), loperamide 1 nM, 10 and 50 μM, and combinations of the loperamide concentrations with IL-1β. Cells were pre-incubated with loperamide for 1 hour prior to the addition of IL-1β. After 5 hours, the supernatant was harvested and IL-8 measured using ELISA. The effect of loperamide on IL-8 expression was also examined by RT-PCR. Naloxone (10 μM) was used as an opioid receptor antagonist.
RESULTS: Caco-2 cells constitutively express mu and kappa opioid receptors. Pre-incubation with loperamide 10 and 50 μM† led to increased IL-8 secretion compared to IL-1β stimulation alone [202 ± 62 vs 92 ± 6 pg/ml and 157 ± 12 vs 92 ± 6 pg/ml, respectively († p=0.005)]. Furthermore, the 50 μM loperamide concentration significantly increased IL-8 mRNA compared to the IL-1β stimulus alone. Increased IL-8 secretion with loperamide 10 and 50 μM was reversible with naloxone.
CONCLUSIONS: Loperamide significantly increases IL-8 secretion in Caco-2 cells stimulated with IL-1β. This effect is reversible with naloxone. Increased IL-8 secretion by loperamide in Caco-2 cells appears to be mediated through mu or kappa receptors.
Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 31, 2000.

Geriatrics

77. Prevalence of Alzheimer's disease and medication utilization in a long-term care setting. *Alisa K. Keene, R.Ph.,* Andrea J. Ries, Pharm.D.; Sterling HealthCare Services, Inc., Shreveport, LA; Pfizer, Inc., Athens, TX.

PURPOSE: This study evaluated the prevalence of Alzheimer's disease (AD) in a long-term care (LTC) setting and reviewed the current medication utilization patterns for these patients. Additionally, the number of elderly patients with potentially undiagnosed AD using age-specific prevalence rates from population surveys was estimated.
METHODS: Patients ≥ 65 years of age from 11 LTC facilities were reviewed for a diagnosis of AD or dementia (ICD-9-CM code 331.0 and 290.0-290.3, inclusive). Patient age, gender, diagnosis code, length of time in nursing home, and AD and other psychotropic medication information were collected.
RESULTS: A total of 1036 patient records were reviewed (males, n=318; females, n=718). A total of 288 (27.8%) patients had a diagnosis of AD. The prevalence of AD by age group in this LTC population was: 65-74 years, 21.8%; 75-84 years, 29.0%; and ≥ 85 years, 29.9%. The observed number of patients with AD for age groups 65-74 years and 75-84 years exceeded the expected number of patients with AD (50 vs 7 and 110 vs 71, respectively) based on prevalence rate estimates from population surveys. Fewer patients ≥ 85 years of age were observed to have AD than expected (128 vs 202). Of the patients ≥ 85 (n=428), 17.3% (n=74) may have undiagnosed AD. Only 49 patients (17%) with AD were on cholinesterase inhibitor therapy. Of these, over 75% receiving donepezil. A total of 56 patients were receiving benzodiazepines (n=15), haloperidol (n=15), risperidone (n=23), olanzapine (n=8), and miscellaneous antipsychotics (n=5). Ten patients were receiving 2 medications.
CONCLUSIONS: Appropriate interventions should be developed to improve recognition and diagnosis of AD in patients ≥ 85 years of age. Opportunity exists to enhance drug therapy for AD patients in this setting.

79. Preventable drug-related morbidity in older adults: development of clinical indicators and identification of risk factors and intervention

strategies. *Neil J. MacKinnon, Ph.D., R.Ph.,* Heather Robertson, M.S., Robert S. Tonks, Ph.D.; Dalhousie University College of Pharmacy, Halifax, N.S., Canada; Queen Elizabeth II Health Sciences Centre, Halifax, N.S., Canada.

PURPOSE: Drug-related morbidities (DRMs) occur frequently in older adults. Fortunately, many are/should be preventable. This study had three primary objectives: 1) to create indicators of *preventable* drug-related morbidity (PDRM) in older adults, 2) to identify risk factors for PDRM, and 3) to formulate strategies to reduce PDRM.
METHODS: The Delphi technique was used with an expert panel of geriatricians and an expert panel of clinical pharmacologists to create indicators of PDRM in older adults in the winter of 2001. In spring 2001, twelve general practitioners (GPs) evaluated the PDRM indicators proposed by the two expert panels and identified risk factors for PDRM. Finally, through the use of a mail survey, all three groups suggested strategies to reduce PDRM.
RESULTS: The two expert panels proposed 58 indicators of PDRM in older adults following two rounds of the Delphi technique. The GPs agreed with 89.7% of the PDRM indicators. Patient issues (such as compliance and socio-economic status), physician issues (such as lack of physician time and knowledge about drugs), and communication with the patient and health professionals were identified as being the most important risk factors for PDRM by the GPs.
CONCLUSIONS: This study has produced indicators of PDRM in older adults, hitherto unavailable in Canada. Pharmacists could use these indicators to proactively identify patients at risk for PDRM. With the risk factors for PDRM and strategies to optimally reduce DRMs identified by our research, such information should help pharmacists and physicians to improve the quality of care provided to older adults.

80E. Health literacy and medication use among community dwelling seniors. *Cynthia L. Raehl, Pharm.D.,* C.A. Bond, Pharm.D., Rebecca B. Sleeper, Pharm.D., Teresa L. Sterling, Pharm.D., Roland A. Patry, D.Ph.; Texas Tech University Health Sciences Center, Amarillo, TX.

PURPOSE: This observational pilot study evaluated the health literacy of community dwelling seniors and the relationships between literacy and medication use.
METHODS: Persons aged 65 and older with corrected vision of at least 20/200 and who passed a hearing screening test were interviewed in their homes to ascertain: demographics (age, education, medical and medication history) and ability to read. Two standardized health literacy tests, the REALM (Rapid Estimate of Adult Literacy in Medicine) and the S-TOFHLA (Short Test of Functional Health Literacy in Adults), along with the Geriatrics Depression Scale (GDS) and Mini Mental Status Exam (MMSE) were administered in random order. The REALM (word recognition test) and S-TOFHLA (reading comprehension test) generally required 2 and 7 minutes respectively.
RESULTS: 34 seniors (age 82.9 ± 5.6 years) completed all study tests. Subject demographics included: highly educated (13.2 ± 2.5) years formal education, MMSE 26.1 ± 3.0, GDS 7.0 ± 5.2, and 5.3 ± 3.0 prescription medications, 4.3 ± 2.5 nonprescription medications and 0.6 ± 0.9 herbal products. Of the 34 subjects, 11 had inadequate functional health literacy, 4 marginal health literacy, and 19 adequate health literacy as assessed by S-TOFHLA. In contrast, REALM results indicated 29 subjects read at the high school level, and 5 at the 7th to 8th grade level. The correlation of the two reading tests was poor (r=0.219, p=NS). Significant positive correlations were found between: REALM and number of herbals (r=0.433, p, 0.01), S-TOFHLA and age (r=-0.576, p<0.0001), S-TOFHLA and education (r=0.347, p<0.05), S-TOFHLA and MMSE (r=0.431, p<0.01).
CONCLUSION: The REALM and S-TOFHLA are poorly correlated in seniors with the REALM overestimating the reading ability of seniors.
Presented at the 2001 Annual Scientific Meeting of the American Geriatrics Society, Chicago, IL, May 10, 2001.

81. Individualized performance-based medication use assessment: the MedTake test. *Cynthia L. Raehl, Pharm.D.,* CA Bond, Pharm.D., Rebecca B. Sleeper, Pharm.D., Roland A. Patry, D.Ph., Tresa Woods, M.S.; Texas Tech University Health Sciences Center, Amarillo, TX.

PURPOSE: The MedTake test was developed to explore how seniors' ability to take their prescription medications may correlate with age, cognitive impairment, depression, and self-management of medications.
METHODS: This cross sectional study was conducted in a retirement community and adult day care center. Comprehensive interviews preceded performance based medication use assessment. MedTake performance test evaluated: 1) dosage, 2) indication description, 3) food or water co-ingestion, and 4) regimen. Each prescription MedTake test was scored as percent of correct actions, equally weighted, compared to vial label directions. A second Pharmacist Medication Use Risk Assessment Score (RPh Risk Score) was assigned for each medication as one of 4 categories: correct use, partial correct use without clinical significance, partial correct use with clinical significance, or incorrect use.
RESULTS: 57 seniors aged 79.5 ± 7.3 years, education 11.3 ± 3.9 year, 71% female completed this study. The MedTake and Risk Score had good correlation (r=0.48, p<0.001). The MedTake test was not associated with education level, overall health estimate, GDS, or MMSE scores. The RPh Risk Score was associated with gender (p=0.01), education (p= 0.01), overall health estimate (p=0.024), number Rx meds (p=0.001), race (p<0.001), patient's own medication management (p<0.001), lives alone (p=0.01), uses medication reminder systems (p=0.012), and marital status (p<0.001).
CONCLUSIONS: Although the quantitative MedTake and qualitative Pharmacist Risk Scores had good correlation, discordant results for individuals suggest both approaches may be necessary to truly assess the ability of seniors to safely take their own prescription medications.

82. Noncompliance with amiodarone monitoring in a nursing home population. James P. Tsikouris, Pharm.D., Alexander P. Tsikouris, Pharm.D., *Bradley E. Hein, Pharm.D.,* Chad R. Worz, Pharm.D.; Texas Tech University, Lubbock, TX; University of Cincinnati, Cincinnati, OH; Skilled Care Long-Term Care Pharmacy, Cincinnati, OH.

PURPOSE: Many elderly nursing home patients with cardiac arrhythmias are treated with amiodarone therapy. Amiodarone causes various organ toxicities, requiring diligent monitoring at least every 6 months for the first year. This retrospective pilot investigation evaluated compliance with recommended monitoring parameters of non-cardiac toxicities with amiodarone in elderly nursing home patients.
METHODS: Medical records of 20 patients receiving chronic amiodarone therapy were reviewed. Monitoring compliance of liver function tests (LFTs), chest x-ray (CXR) for pulmonary toxicity, thyroid function tests (TFTs), and ocular exams was determined at usual recommended time points (baseline, 6 months, and 1 year).
RESULTS: Information available for all 20 patients revealed poor compliance with ordering baseline LFTs (15%), CXR (30%), TFTs (25%). Six-month information was available for 16 of 20 patients, and remained suboptimal: LFTs (13%), CXR (13%), and TFTs (25%). In 9 patients receiving one year of amiodarone, only 3 patients had LFTs performed, 2 had CXR performed, and 2 had TFTs performed at the one-year time point. No patients received ocular exams at any time.
CONCLUSIONS: This first investigation of amiodarone monitoring compliance in elderly nursing home patients illustrates that there may be inadequate monitoring for severe adverse effects in these patients. Often limited physician contact, unfamiliarity with adverse effects, and previously documented suboptimal care of some nursing home patients likely contributed to the observed noncompliance of amiodarone monitoring. In addition to education of physicians and pharmacists, implementation of practice guidelines for amiodarone monitoring could help prevent and manage associated complications.

83. Impact of inappropriate prescribing defined by DUR criteria on health services utilization in community dwelling elders. Joseph T. Hanlon, Pharm.D., M.S., Gerda G. Fillenbaum, Ph.D., Bryan Dowd, Ph.D., Lawrence R. Landerman, Ph.D., Margaret Artz, Ph.D., Cynthia Gross, Ph.D., Heidi O'Connor, M.S., Charles Boult, M.D., MPH, MBA, Judith Garrard, Ph.D., Kenneth Schmader, M.D.; University of Minnesota, Minneapolis, MN; Duke University, Durham, NC.

PURPOSE: The impact of inappropriate drug prescribing, as defined by HCFA expert consensus panel criteria for dosage, duplication, drug-drug interactions and duration, and US and Canadian expert consensus panel criteria for drug-disease interactions, on health service use was examined in older community dwelling elders.
METHODS. Inappropriate prescribing was determined using drug use data for eight medication classes (digoxin, calcium channel blockers, angiotensin converting enzyme inhibitors, histamine$_2$ receptor antagonists, nonsteroidal anti-inflammatory drugs, benzodiazepines, antipsychotics, and antidepressants) from the 1989-90 wave of the Duke Established Populations for Epidemiologic Studies of the Elderly survey (n=2684). Outcomes were measured up to three years later using HCFA Medicare Part A files for hospital admissions and self-reported nursing home admission and outpatient visits.
RESULTS: While 20.0% were prescribed inappropriate drugs, in multivariate analyses they did not have an increased likelihood of hospitalization (Adj HR 1.08; 95% CI 0.90, 1.31); longer stay (b coeff. -0.09; 95% CI -0.48,0.28) or higher cost (b coeff. 0.09; 95% CI -0.26,0.45) when hospitalized; earlier nursing home admission (HR 1.06; 95% CI 0.76,1.47) or longer stay there (Adj OR 1.12; 95% CI 0.67,1.88). However, inappropriate prescribing was significantly associated (p<0.05) with more outpatient visits (b coeff. 0.82; 95% CI 0.27, 1.37) and the strength of this relationship increased for those with a potential drug-drug or drug-disease interaction problem (b coeff. 1.25; 95% CI 0.45, 2.00).
CONCLUSIONS. Inappropriate prescribing defined by DUR criteria was associated with multiple physician outpatient visits. Potential drug-drug and drug-disease interactions had more pronounced effects.

84. Vitamin and mineral supplement use among older Americans. *Jacqueline S. Marinac, Pharm.D.,* Colleen Buchinger, M.C., Lincoln Godfrey, D.O., James Wooten, Pharm.D., Sandra Willsie, D.O.; University of Health Sciences; University of Missouri at Kansas City; Truman Medical Center-West, Kansas City, MO.

PURPOSE: Estimates suggest 85% of older Americans are at risk for malnutrition. Iron, folate and B-12 anemias are more common in the elderly. The purpose was to survey inner city Americans regarding current use of vitamin and mineral supplements.
METHODS: 267 Americans over age 60 were recruited for the face-to-face survey. Data were stratified by gender, ethnicity, economic status and education.
RESULTS: 70% surveyed were female, 50% Caucasian and 49% African American (AA). 23% had less than HS education, 36% completed HS and 35% had over 12 years schooling. Fifty-five percent had a total family household income of $10-20,000, 28% over $20,000 annually. Eighty-seven percent were under a doctor's care. A multivitamin (MVI) was taken by 40%, vitamin E 21% calcium 21%, vitamin C 16%, vitamin D 6%, vitamin B-12 4%, vitamin A 4%, B-Complex 3%, magnesium 3%, iron 2%, pyridoxine 1%, and zinc 1%.
More females take a MVI and calcium ($p<0.05$). Significantly more white adults are taking MVI, Ca++, Vitamins C and E ($p<0.05$) over AA. Greater Ca++, Vit C and E use was reported by those with the highest education ($p<0.05$). Greater income was associated with Vit C and E use ($p<0.05$).
CONCLUSIONS: Approximately 40% take a MVI supplement, yet only 15% males reported any vitamin/mineral use. One in five take vitamin E, C, and calcium. Only 29% of women are taking calcium. AA consume significantly less vitamins/minerals than Caucasians. Pharmacists may assist older patients in proper selection and safe use of supplements.

85. Drug interactions and health care costs in treating Alzheimer's disease patients. *John Rizzo, Ph.D.*; Ohio State University, Columbus, OH.

PURPOSE: To assess the impact of drug interactions due to concomitant medication usage in Alzheimer's disease (AD) populations and the resulting impact on total health care costs.
METHODS: 1999 MarketScan data were obtained. In this database, 2955 Medicare patients with diagnosis codes for Alzheimer's disease were identified. This sample was further divided into two cohorts: patient treated with donepezil (n=1674) and those without (n=1281). Through literature review, the top ten drugs most likely to interact with donepezil were identified and a binary variable was created for each drug to indicate whether a patient was on this potentially interacting drug. A multivariate regression model was developed using the natural log of the total health care costs of patients as the dependent variable. The explanatory variables in the model were demographic variables, comorbidity variables, donepezil-interacting drug variables, a binary variable indicating whether patients were on donepezil, and interaction terms between the donepezil variable and others.
RESULTS: Eight of ten interacting drugs showed a greater impact on total health care cost for AD patients for donepezil patients than for non-donepezil patients. Four of these eight drugs (i.e., ranitidine, haloperidol, diltiazem, and paroxetine) significantly increased total health care costs of AD patient who were on donepezil, raising health care costs per patient-year by $3287 for ranitidine, $1620 for haloperidol, $1356 for diltiazem, and $672 for paroxetine. However, those four drugs had no significant impact on costs for non-donepezil patients.
CONCLUSIONS: These potential drug-drug interactions with donepezil increase total health care cost of AD patients. Patients on multiple drugs should be treated with caution when prescribed donepezil.

86. Cost effectiveness of low molecular weight heparin and unfractionated heparin in the treatment of deep vein thromboses in long-term care residents. *Shyam D. Karki, Pharm.D., M.A.,* Terrance J. Bellnier, B.S., MPA, Joshana Karki, Pharm.D., William R. Patterson, B.S., Gule-Rana Masood, M.D.; State University of New York at Buffalo, Buffalo, NY; Clifton Springs Hospital & Clinics, Clifton Springs, NY.

PURPOSE: Nursing home residents with acute proximal deep-vein thrombosis (DVT) are usually transferred to the hospital and treated initially with unfractionated heparin administered by continuous infusion for 4-6 days. The anticoagulant response to this treatment varies markedly and the dosage is adjusted by measuring the activated partial-thromboplastin time closely. With the proven efficacy and safety of low molecular weight heparins in treatment and prophylaxis of deep vein thrombosis and no need to closely monitor any parameter and adjust the dosage, it has become possible to treat DVT in nursing home setting. We describe our findings of the economic implications of two different therapies.
METHODS: All residents treated for DVT in the last 2 years were identified and their charts reviewed as to the use of heparin or enoxaparin (formulary LMWH in our institution). Charts of 50 residents from each group matched for sex and age were randomly reviewed as to efficacy, transfer to hospital, days of hospitalization and costs of treatment.
RESULTS: The residents, in the heparin arm, were transferred to the hospital, treated with continuous heparin infusion, initiated on warfarin therapy and then transferred back to the nursing home. The average length of the hospitalization was 5 + 1 days and the mean hospitalization cost was $4450 + 870. All residents on enoxaparin arm were treated in the nursing home and their costs calculated for first 5 days of treatment were $1600 + 320. Thus there was a cost saving of $2850 per resident in the enoxaparin arm.
CONCLUSION: Our results indicate that enoxaparin is cost effective in the treatment of DVT in the nursing home residents. However under the current reimbursement system, there is disincentive to treat DVT in the nursing home.

87E. Adverse reaction among patients with Alzheimer's disease using rivastigmine and donepezil. *Roger Luo, Ph.D.*; University of Southern California, Los Angeles, CA.

PURPOSE: To study adverse reaction profiles of rivastigmine and donepezil for patients with Alzheimer's disease.
METHODS: A retrospective study was conducted using the 2000 FDA Quarterly Data from the Adverse Event Reporting System (AERS). To estimate the number of patients prescribed each of these two drugs, we utilized prescription and sales data. Adverse drug reaction measures were calculated as proportions of the adverse events to each category. Statistical analyses were performed to test differences in the proportions.
RESULTS: For rivastigmine, the most frequent adverse reactions were nausea and malaise; for donepezil, they were drug interactions and convulsions. No statistically significant difference between rivastigmine and donepezil had been detected in the total rates of adverse reactions and serious adverse drug reactions (as defined by FDA). However, the rate of common adverse events for donepezil was significantly higher as compared to its product labeling ($p<0.05$). Adverse events due to drug interaction was significantly higher for donepezil ($p<0.05$).
CONCLUSIONS: Efficacy and concomitant medication usage should be considered by physicians for choosing therapies treating Alzheimer's disease.
Presented at the 126th Annual Meeting of the American Neurological Association, Chicago, IL, September 30 - October 3, 2001.

88. Use of inhaled respiratory medications by wet nebulization in Nova Scotia seniors under Pharmacare's Reimbursement Guidelines. *Susan K. Bowles, Pharm.D., M.Sc. student,* Ingrid Sketris, Pharm.D., MPA (HAS), George Kephart, Ph.D.; Drug Evaluation Alliance of Nova Scotia, NS, Canada; Dalhousie University, Halifax, NS, Canada.

PURPOSE: During 1999, approximately 5000 beneficiaries of the Nova Scotia Seniors' Pharmacare Program received respiratory medications by wet nebulized therapy (WNT), at a cost of over $2 million dollars (Canadian)/year. On August 1, 2000, guidelines for the reimbursement of WNT were implemented. We examined approved reimbursement requests to determine patient demographics, reasons for using WNT and the type of physician making requests.
METHODS: 200 approved requests for WNT therapy were randomly selected, 28 were excluded due to coverage by another program and 172 were reviewed for a 10-month period after implementation of the guidelines.
RESULTS: 98% of all requests were made by family physicians. Males and females represented 44% (mean age 77 ± 8 years) and 56% (mean age 79 ± 9 years) of requests, respectively. 27% of requests were for nursing home residents. The most frequently cited reasons for using WNT included inability to use dry inhaler devices (DIDs) due to dementia or physical disability (56%), poor inspiratory capacity (16%) or for short-term use in palliative care or during an acute illness (9%). 48% were using both WNT and DIDs.
CONCLUSIONS: Family physicians were responsible for almost all requests for WNT. Most patients using WNT were reported to be unable to use DIDs. The proportion using both DIDs and WNT suggests sub-optimal use of DIDs in some individuals. Further work is needed to determine patient and physician attitudes/preferences about WNT and DIDs, as well as the policy impact on health outcomes and utilization of health care services.

89E. Development of a tool to assess the geriatric patient's ability for self-medication. Debbie L. MacLeod, B.Sc.Pharm., *Priti S. Flanagan, B.S.P.,* Pharm.D., Douglas French, Ph.D.; South-East Health Care Corporation, Moncton, NB, Canada.

PURPOSE: Several methods for detecting medication non-adherence have been reported; however, there is limited research on predicting adherence rates. The objectives of this study were to develop and test a method to assess cognitive capability to self-medicate in geriatric patients who are functionally able and to determine whether this test is predictive of adherence.
METHODS: Eligible study participants were taught about their discharge medication regimen and then tested on the information provided using a scored questionnaire (T1). This procedure was followed for a hypothetical medication scenario (T2). Participants were randomly assigned to receive either T1 or T2 first. Within two weeks of hospital discharge, a follow-up visit was performed to re-administer T1 and to count medications. Data analysis was performed using paired samples T-test and Pearson Correlation.
RESULTS/CONCLUSIONS: Twenty-one patients completed the study. Scores on T1 were significantly higher than scores on T2 ($p<0.001$). At home test scores were significantly related to MMSE score ($p=0.031$), complexity of medication regimens ($p=0.004$) and T1 scores ($p<0.001$). Adherence rates were found to correlate with MMSE ($p=0.012$). The assessment tool (T1) predicted a participant's cognitive understanding of their medication regimen. Furthermore, MMSE scores may be useful in predicting medication adherence. Additional study is required to assess the correlation between T1 scores and medication compliance over time.

Presented at the Annual General Meeting of the Canadian Society of Hospital Pharmacists, Halifax, NS, Canada, August, 2001.

90E. Underutilization of cardiac medication therapy in diabetic elderly outpatients at a veterans affairs medical center. *Deborah H. Kennedy, Pharm.D.,* Mel C. Magboo, M.D., Christine M. Ruby, Pharm.D., Jack I. Twersky, M.D.; Nova Southeastern University, Fort Lauderdale, FL; Nevada Rural Health Centers Inc., Carson City, NV; Duke University, Durham, NC; Durham Veterans Affairs Medical Center, Durham, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC.

PURPOSE: To establish the prevalence of cardiac medication therapy underutilization in elderly diabetic outpatients.
METHODS: Sixty diabetic patients greater than 74 years of age, who were enrolled in Primary Care or Geriatrics clinics for at least one year and seen July 1999 through December 1999, were randomly chosen for inclusion. A clinical pharmacist and physician independently conducted a retrospective abstracted chart review of patient information. The number of cardiac medications that were indicated, but absent from the medication regimen was determined.
RESULTS: The average age was 79.4 years. Per patient, the average number of medications used was 8.3, number of disease states was 7.0, number of cardiac conditions evaluated was 2.7, and number of cardiac conditions with underutilization was 1.0. Thirty-seven (62%) of patients had at least one cardiac condition with underutilization of medication.
CONCLUSIONS: Cardiac medications were underutilized in diabetic elderly outpatients. Larger studies should be conducted in non-veteran populations to determine the prevalence of the underutilization of medications in the elderly.
Presented at the Midyear Clinical Meeting of the American Society of Health-System Pharmacists, Las Vegas, NV, December 3-7, 2000.

91E. Pharmacokinetics of vardenafil (a new selective PDE5 inhibitor) in the elderly and subgroup data on efficacy and safety in elderly patients with erectile dysfunction. *Christopher P. Steidle, M.D.,* Richard A. Feldman, M.D., John Lettieri, Ph.D., Vipin Agarwal, Ph.D., Thomas Segerson, M.D.; NE Indiana Research LLC, Fort Wayne, IN; Urology Specialists, Hartford, CT; Bayer Corp., West Haven, CT.

PURPOSE: To evaluate the pharmacokinetics (PK), the efficacy and tolerability of vardenafil in the elderly.
METHODS: In a pharmacokinetic (PK) study, healthy men ages 18 to 45 (n= 9) and >65 (n=9) were given a single oral dose of 40 mg vardenafil. In a double-blind, randomized at-home phase II study, men <45 years (n=134) or >65 years (n=65) with mild to severe erectile dysfunction received placebo, 5 mg, 10 mg or 20 mg vardenafil for 12 weeks. Efficacy was evaluated using the International Index of Erectile Function B Erectile Function Domain (IIEF-EF).
RESULTS: In the PK study, mean C_{max} and $AUC_{0\text{-}tn}$ were 34 % and 52 % greater for the men >65 years. T_{max} was similar (0.6 h and 0.5 h) and the $t_{1/2}$ was slightly more prolonged for the older men (6.0 h versus 4.8 h). No clinically significant changes in heart rate or blood pressure were observed. Adverse events were primarily headache, rhinitis, nausea, dyspepsia and flushing. In the at-home phase II study, mean IIEF-EF changes from baseline for men <45 years were 1.1, 7.9, 8.4 and 8.1 for placebo, 5 mg, 10 mg and 20 mg, respectively. For patients over 65, the corresponding increases from baseline were 0.5, 2.5, 7.8, and 10.3. At least one adverse event (not necessarily treatment-related) was experienced in 29-39% men < 45 years and in 29-63% for men >65 years, with no clear dose relationship.
CONCLUSION: This study shows that men > 65 years tended to have slightly increased plasma levels and had similar improvements in IIEF scores compared to men < 45 years old.
Presented at the Annual Meeting of the American Geriatrics Society, Chicago, IL, May 9-13, 2001.

92. Improving patient outcomes in a medication assistance program: a study in pharmaceutical care. *Stephanie N. Kiser, R.Ph.,* Nikita H. Patel, Pharm.D.; Mission St. Joseph's Hospitals, Asheville, NC.

PURPOSE: In the United States, there is a growing number of elderly that have inadequate prescription coverage. In 1998 the Mission St. Joseph's Medication Assistance Program for Seniors (MAP) was developed to address this problem in our local community. The purpose of the program is to provide medications, education, and disease state management for Medicare recipients at or below 120% of the federal poverty level. A pharmaceutical care model is utilized to provide continuity of care to high-risk elderly. The program objectives include improved clinical and economic outcomes in addition to quality of life.
METHODS: MAP utilizes "Informacare" pharmaceutical care software for patient documentation. SF-12 and ADL surveys are administered with each enrolled patient. Patient data is evaluated to determine readmission rates, ER visits, and losses to the health system.
RESULTS: Evaluation of yearly data prior to and post enrollment has revealed a reduction in hospital readmission rates from 28 prior to 15 post. This has resulted in decreased monetary losses to our health system from minus $260,000 prior, to minus $40,000 post. A review of quality of life data is ongoing.
CONCLUSIONS: Our program model reiterates the need for a pharmacist's role in medication management for ambulatory patients. Preliminary analysis indicates an improvement in clinical and economic outcomes. Adverse medication events could be prevented through the development of more programs that incorporate the supplying of needed medications with pharmaceutical care.

Health Services Research/Managed Care

93. Prescription access programs offered by health care systems and organizations on a regional and national level. *James D. Nash, Pharm.D.,* Martin R. Giannamore, Pharm.D., Milap C. Nahata, Pharm.D.; Ohio State University; Pfizer, Inc., Columbus, OH.

PURPOSE: Millions of Americans have no access to prescription drugs. Our purpose was to identify prescription assistance programs for indigent/uninsured patient populations across the United States, and to determine how these programs address barriers to prescription access.
METHODS: A survey was sent to 93 agencies throughout the country, which included regional and national programs. Data were analyzed using Microsoft Access 97.
RESULTS: About 81% of the surveys were completed and returned. Both national and regional programs reported to serve primarily adult patient populations. Eligibility for the majority of the programs was determined by financial means. Sixty-five percent of programs dispensed and/or prescribed medications with a monthly average of 1170 prescriptions dispensed at no cost to the patient. Medication assistance was provided by 86% of the programs, primarily through the use of manufacturer supported indigent care programs (34%) and samples (25%). Ninety-four percent of programs referred patients to outside organizations for assistance with the cost of various medications. Education regarding medication compliance and proper medication use was offered by 76% of the programs. Pharmacists were responsible for providing this education in 34% of programs. Individualized patient counseling was the most common method of education utilized by 43% of the programs. The agencies indicated that providing sample medications was of greatest benefit to the individuals requesting medication assistance.
CONCLUSIONS: Various methods were used to provide access to prescription medications for patients. The majority of programs relied on manufacturer supported indigent care programs and samples. The programs frequently referred patients to other organizations to obtain medications.

94. Family physicians' reasons for not enrolling eligible patients into a pharmacy-initiated clinical trial. Bita Bateni, B.Sc.Pharm., M.Sc. candidate, Stephen J. Shalansky, Pharm.D.; St. Paul's Hospital, Vancouver, BC, Canada; University of British Columbia, Vancouver, BC, Canada.

PURPOSE: To determine family physicians' reasons for not enrolling eligible patients into a pharmacy-initiated clinical trial. The trial was designed to compare a new community pharmacy-based anticoagulation service to standard care.
METHODS: Surveys were mailed to all family physicians who had been invited to enroll patients in the clinical trial: 8 who had agreed to enroll and 110 who did not. Physicians were asked to rank the most important reasons why they did or did not participate, and the extent to which they agreed with specific statements describing potential concerns with the study. Responses were anonymous. A $50 check was included with all surveys, and reminders were sent at 2 and 4 weeks.
RESULTS: The response rate from physicians had not agreed to enroll patients was 73%. Most of these respondents had five or more warfarin patients in their practice (83%), and only one had no eligible patients. Most had participated in 1 to 5 previous clinical trials (51%), while 38% had no previous trial participation. The three most important reasons for not enrolling patients included "no time to review materials" (18%), "want to remain responsible for my patients" (13%), and "concern about healthcare professionals taking over physician responsibilities" (13%). The response rate from physicians who agreed to enroll patients was 100%, and the most important reason for agreeing to participate was "research advances the profession" (87%).
CONCLUSIONS: Family physicians may be reluctant to enroll patients in clinical trials that involve pharmacists taking on additional responsibility for patient care.

95. Promoting medication safety and detecting non-adherence through pharmacy claims. *Nella Bieszk, Pharm.D.,* Rosalie Patel, Pharm.D., Andrea Heaberlin, Pharm.D., Ken Wlasuk, R.Ph., Barbara Zarowitz, Pharm.D., BCPS, FCCP; Pharmacy Care Management; Henry Ford Health System, Detroit, MI.

PURPOSE: To assess the impact of providing physicians with patient pharmacy claims data during the patient's office visit on: time required to obtain a medication history, detection of improper medication use, likelihood of medication review and subsequent changes and adherence to a preferred

formulary.
METHODS: A prospective, concurrent, single-blind study. Pharmacists provided claims data (six-month medication history) to internal medicine physicians for patients with scheduled clinic appointments. Data for control patients, generated on alternate days, was not supplied to physicians. A blinded abstractor reviewed dictated office notes for control and active cases to obtain data necessary to compare the two groups. Surveys were distributed to physicians to assess their impression on the ability of claims data to improve quality of care.
RESULTS: Two hundred thirty one patient visits were analyzed; 105 active and 126 control. The abstractor detected a non-adherence rate of 57.1% in the control group and 58.1% in the intervention group, p=NS). Physicians detected no non-adherence in the control group versus 30.5 % in the intervention group (p<0.001). Medication regimen changes occurred more often in the intervention group (p<0.001). The mean number of non-preferred drugs switched to preferred drugs differed between the intervention and control groups (27.7% vs 0.0%, p<0.001). Surveys returned (59/105) indicated a reduction in the time to obtain an accurate medication history in 50% of cases.
CONCLUSIONS: Providing accurate pharmacy claims data to physicians during the office visit is an effective means of detecting non-adherence, improving formulary compliance, and integrating medication review into the ambulatory care of patients.

Hematology/Anticoagulation

96. Pentasaccharide, the first selective factor Xa inhibitor, offers superior prevention of venous thromboembolic events after orthopedic surgery compared with low molecular weight heparin. Alexander G.G. Turpie, M.D., Kenneth A. Bauer, M.D., Bengt Eriksson, M.D., Michael R. Lassen, M.D., *David W. Hawkins, Pharm.D.*; Hamilton General Hospital–McMaster Clinic, Hamilton, ON, Canada; Beth Israel Deaconess Medical Center, Boston, MA; Sahlgrenska University Hospital, Göteborg, Sweden; Hilleroed Hospital, Copenhagen, Denmark; Mercer University, Atlanta, GA.

PURPOSE: A large clinical program evaluated efficacy and safety of pentasaccharide (fondaparinux sodium, Arixtra®), a novel synthetic factor Xa inhibitor, compared with enoxaparin, a low-molecular-weight heparin (LMWH), for venous thromboembolism (VTE) prevention following major orthopedic surgery.
METHODS: In 4 prospective, randomized, double-blind, multicenter phase III trials, involving >7000 patients hospitalized for hip replacement (Pentathlon 2000 and Ephesus), hip fracture (Penthifra), and major knee surgery (PentaMaks), patients randomly received pentasaccharide 2.5 mg subcutaneously (SC) once daily starting postoperatively or enoxaparin according to approved regimens for 7±2 days. Primary efficacy outcome was adjudicated VTE up to day 11 (deep vein thrombosis [DVT] detected by mandatory bilateral venogram or documented symptomatic DVT or pulmonary embolism). The primary safety outcome was defined as fatal bleeding, nonfatal bleeding in a critical organ, bleeding requiring reoperation, or overt bleeding with a bleeding index ≥2 (based on transfused units and pre- and post-bleed hemoglobin levels).
RESULTS: Pentasaccharide significantly reduced overall VTE risk by 55.3% (*P* values: 10^{-17} common odds ration test and 0.16 homogeneity test) compared with enoxaparin, with a decrease in total and proximal DVT events. Similar safety profiles, in terms of clinically relevant bleeding, were observed for the 2 agents.
CONCLUSION: In major orthopedic surgery, pentasaccharide (fondaparinux sodium, Arixtra®) 2.5 mg SC once daily demonstrates superior efficacy with similar safety compared with enoxaparin for VTE prophylaxis and may offer significant therapeutic improvement over existing antithrombotic regimens.

97. Low-molecular-weight heparins: development of a therapeutic interchange program. *Kimberly Davis Nolen, Pharm.D.*; South Fulton Medical Center, East Point, GA.

OBJECTIVE: Primary objective is to determine which low molecular weight heparin (LMWH) is the most cost-effective based on clinical data to support its use as the sole LMWH on formulary at our institution. Secondary objective is to develop a therapeutic interchange program for the LMWHs.
METHODS: First the FDA indications and dosing strategies of the two LMWHs, enoxaparin and dalteparin, were reviewed. Tinzaparin had just received approval and was not on our formulary, so this drug was not evaluated. The clinical trails were reviewed for all the FDA indications to help determine which drug had the more solid data to support its use. The Chest guidelines were reviewed to ensure that our program followed the ACCP Consensus Conference on Antithrombotic Therapy. Lastly, medication utilization evaluations (MUE) on both dalteparin and enoxaparin were performed.
RESULTS: Based on the MUE, there was 70% enoxaparin and 30% dalteparin usage in our facility. Based on FDA indication, enoxaparin was used correctly 62% (26/42) of the time and dalteparin 30% (6/20). Enoxaparin and dalteparin were dosed appropriately 70% and 67% of the time, respectively. Based on the patients receiving enoxaparin 30 mg q12h, 92% (22/24) would have been eligible for the 40 mg QD dose.
CONCLUSION: Enoxaparin was chosen as our sole LMWH on formulary. Enoxaparin had all six of the FDA indications and the clinical trials showed a trend toward better efficacy against the current standards. Based on the acquisition costs for both LMWHs and the fact that we were not going to receive any discounts based on our market share of 70%/30% for enoxaparin and dalteparin, respectively, an approximate annual cost saving of $47,000 was predicted by using enoxaparin only. A therapeutic interchange program was developed and approved by both the P&T committee and the Medical Executive Committee, so that patients eligible for the 40 mg QD of enoxaparin and orders written for dalteparin could automatically be changed by pharmacy.

98. The first selective factor Xa inhibitor, pentasaccharide, demonstrates a highly favorable pharmacokinetic profile in young and elderly healthy subjects. Francois Donat, Jean-Pierre Duret, Alix Santoni, Roger Cariou, Jose Necciari, Harry N. Magnani, Rik de Greef, *David W. Hawkins*; Sanofi-Synthelabo, Inc., Paris, France; Organon, Inc., Paris, France; Mercer University, Atlanta, GA.

PURPOSE: Venous thromboembolism (VTE) incidence increases with age, and more effective antithrombotic therapies are needed for VTE prophylaxis in geriatric populations. Pentasaccharide (fondaparinux sodium, Arixtra®) is the first of a novel class of synthetic, selective factor Xa inhibitors. Unlike low-molecular-weight heparins it is a single chemical entity without any animal-sourced components and its plasma concentration is measured by a validated bioassay.
METHODS: The pharmacokinetic (PK) profile of pentasaccharide was investigated in healthy subjects in 20 clinical trials conducted in young and elderly men and women, with single or repeated administration.
RESULTS: In young subjects, a single subcutaneous (SC) administration of pentasaccharide 2.5 mg was absorbed rapidly: mean maximum concentration (C_{max}) of 0.34±0.04 mg/L, was reached within 1.7±0.4 hours of dosing, and $C_{max}/2$ was reached 25±5 minutes after dosing, remaining above this value for 11.0±1.4 hours. At the 2.5-mg dose, pentasaccharide's highly reproducible PK profile was confirmed by low intraindividual and interindividual variability estimates for C_{max} (5.5%-11.6%) and area under the curve (AUC, 4.4%-17.5%), respectively. In elderly subjects, after single 2-, 4-, or 8-mg SC or 4-mg intravenous doses, pentasaccharide's complete bioavailability via the SC route was confirmed, as was its dose-independent (linear) PK profile. Data obtained with repeated daily administration were consistent with time-dependent pharmacokinetics: steady state levels obtained after 3-4 days with only minimal increase (1.3-fold) in maximum concentration and AUC_{0-24}.
CONCLUSION: Pentasaccharide therapy offers ease of clinical use, requiring once-daily SC dosing for predictable 24-hour antithrombotic protection, in young and elderly subjects.

99. Pentasaccharide, the novel specific antithrombotic agent: in vitro protein binding to human plasma and purified antithrombin. Francis Paolucci, Marie-Christine Clavies, Francois Donat, Jose Necciari, *David W. Hawkins*; Sanofi-Synthelabo Inc., Paris, France; Mercer University, Atlanta, GA.

PURPOSE: Pentasaccharide (fondaparinux sodium, Arixtra®) is the first of a new class of synthetic antithrombotic agents that selectively inhibit factor Xa. Pentasaccharide binds specifically to antithrombin, the main endogenous regulator of the coagulation cascade. We investigated whether pentasaccharide may specifically bind to other plasma proteins commonly involved in drug binding.
METHODS: We studied in vitro protein binding of pentasaccharide to human plasma and purified antithrombin (at 0.125 mg/ml, the plasma antithrombin concentration commonly reported for normal human subjects) and other purified plasma proteins (e.g., serum albumin, α-1 acid glycoprotein).
RESULTS: At clinically relevant concentrations up to 2 mg/L, pentasaccharide was extensively bound to human plasma (>97%) and purified antithrombin (>94%). At higher concentrations, pentasaccharide binding to human plasma gradually decreased from 95% (at 3 mg/L) to 81% (at 50 mg/L), while the decrease was sharper (91%-27%) for binding to purified antithrombin over the same concentration range. Scatchard analysis of binding in human plasma indicates specific binding to a single site coupled with a nonspecific binding component. Specific binding parameters (maximum binding [B_{max}] and dissociation constant [K_d] were comparable between human plasma (B_{max}=2072 nM, K_d=28 nM) and purified antithrombin (B_{max}=1627 nM, K_d=32 nM). There was no specific binding between pentasaccharide and other purified plasma proteins.
CONCLUSION: In human plasma, at clinically relevant concentrations (≤2 mg/L) pentasaccharide is highly and specifically bound only to antithrombin, and potential interaction with drugs via albumin or α-1 acid glycoprotein displacement is not expected.

100. Clinical and statistical agreement of two point-of-care testing devices versus a reference laboratory for determining the International Normalized Ratio. *Lee J. Bragg, Pharm.D.,* Fran Yanak, R.N., BSN, Kenneth M. Shermock, Pharm.D., Georgann Mazzoli, Pharm.D., Jason Connor, M.S., Kimberly Begany, Pharm.D.; Cleveland Clinic Foundation, Cleveland, OH.

PURPOSE: To evaluate the level of statistical and clinical agreement of two point-of-care testing (POCT) devices (AvoSure PT PRO and ProTime Microcoagulation System) compared to the local reference laboratory for determining the international normalized ratio (INR).
METHODS: Patients taking oral warfarin provided two capillary blood samples for the POCTs and one venous blood sample for the laboratory during a single anticoagulation clinic visit. The level of agreement between each POCT device and the laboratory was evaluated by Bland-Altman style bias plots, concordance coefficient analysis, and clinical agreement. Clinical agreement was assessed as the proportion of agreement between each POCT and the lab in terms of maintenance dosage adjustments (up, down, or no change) as rated by three anticoagulation pharmacy specialists who had each patient's medical and INR history, but were blinded to the source of each INR value.
RESULTS: Both POCTs tended to overestimate INR. The mean bias was slightly lower for AvoSure (0.4, 95% CI -0.6, 1.4) than for ProTime (0.5, 95% CI -0.3, 1.3). Visual analysis of the bias plots indicated systematic error for ProTime; it overestimated low INR values and underestimated high values. Concordance between the lab and the devices were similar (lab and AvoSure 0.82, lab and ProTime 0.76). A greater percentage of INR values from the AvoSure device would have resulted in the same dosing decision as the lab compared with the ProTime device (78% vs 66%, p<0.001).
CONCLUSION: The AvoSure device is associated with less systematic bias and a higher degree of clinical agreement with our reference lab than the ProTime device.

101. Evaluation of the precision of two point-of-care anticoagulation monitors. *Dawn E. Havrda, Pharm.D., BCPS,* Toni L. Hawk, Pharm.D.; University of Oklahoma, Oklahoma City, OK.

PURPOSE: The study evaluated precision of INR results obtained from two point-of-care (POC) anticoagulation monitors, CoaguChek® S (CCS) and Avosure® PT PRO (APP).
METHODS: Precision was evaluated using INRs from patients on warfarin and from liquid quality controls (LQC). Thirty-one patients ≥ 18 years-old providing informed consent and taking warfarin with INRs < 7.0 were included. Parallel assessment of INR was done by obtaining duplicate INRs for each monitor and the laboratory. Nine paired LQC tests, level 1 and level 2, were performed for each POC monitor. Precision was examined by comparing mean difference ± SD between repeated INRs from POC monitors and laboratory (paired t-test, p<0.05) and coefficient of variation.
RESULTS:
For patient samples, the mean difference ± SD for duplicate INRs were 0.16 ± 0.16 CCS; 0.17 ± 0.16 APP; 0.10 ± 0.12 lab (p=0.048, APP vs lab; p=0.082, CSS vs lab). Coefficient of variation was 6% with CCS, 6.5% with APP, and 4.9% with laboratory. When INR values > 4.0 were excluded, coefficient of variation was 4.7% with CCS, 5.7% with APP, and 4.5% with laboratory.
For liquid quality controls, the mean difference ± SD for duplicate INRs for level 1 and level 2 were 0.06 ± 0.10 and 0.18 ± 0.11 for CCS and 0.10 ± 0.06 and 0.17 ± 0.19 for APP, respectively (NSS). Coefficient of variation for level 1 and level 2 was 4.6% and 3.3% for CCS and 6.7% and 5.4% for APP, respectively.
CONCLUSIONS: The CCS had greater precision than APP when comparing duplicate patient INR values to laboratory and with liquid quality controls.

102. Lepirudin anticoagulation in patients with heparin-induced thrombocytopenia who require cardiopulmonary bypass surgery. *Amy L. Seybert, Pharm.D.,* Charlene M. Fabrizio, R.N., Lawrence C. Wei, M.D., Ronald V. Pellegrini, M.D.; University of Pittsburgh Medical Center Health System, Pittsburgh, PA.

PURPOSE: To evaluate lepirudin as an alternative anticoagulant in patients with heparin-induced thrombocytopenia (HIT) who require cardiopulmonary bypass surgery (CPB).
METHODS: A multidisciplinary team consisting of cardiologists, hematologists, perfusionists, cardiac surgeons, laboratory technicians, and a clinical pharmacist developed a protocol for lepirudin dosing during cardiopulmonary bypass surgery. All available literature was utilized to guide dosing and monitoring of lepirudin. Ecarin clotting times (ECT) and thromboelastograms (TEG) were utilized for anticoagulant monitoring during bypass surgery.
RESULTS: Four patients were diagnosed with HIT and required CPB surgery. Three patients had successful anticoagulation during the procedure and recovery. One patient developed significant clot formation. This patient required multiple bolus doses of lepirudin during bypass and also required urgent re-exploration surgery 12 hours post-operatively, due to hemodynamic instability. The patient was found to have patent coronary arteries and grafts. The cause of the hemodynamic instability was unable to be determined.
CONCLUSION: There is minimal data on alternative anticoagulation strategies in patients with HIT who require coronary artery bypass grafting or valve replacement. Lepirudin, which can be monitored with ECTs during CPB surgery, may be an appropriate alternative. Caution must be observed with each patient to maintain adequate anticoagulation. Further study is required to improve safety and efficacy of lepirudin therapy during CPB surgery. Ongoing analysis of HIT patients requiring surgery will take place. Other direct acting antithrombin agents will also be evaluated for utilization in CPB surgery.

Herbal Medicine

103. A survey of dietary supplement use in an urban teaching hospital's outpatient clinics. Darren W. Grabe, Pharm.D., *Gina Garrison, Pharm.D.,* George Eisele, M.D.; Albany College of Pharmacy; Albany Medical Center, Albany, NY.

PURPOSE: Recent data shows increasing use of non-traditional medical alternatives by the American population over the past few years. Despite this trend, the current use in primary care settings and specialty care clinics is unknown.
METHODS: This study was designed to identify current usage patterns of common herbal and dietary supplements in a primary clinic (PC) versus a nephrology clinic (NC). A random selection of 1000 adult patients from each clinic were mailed a questionnaire. The questionnaire was designed to ascertain current use of both herbal and dietary supplements.
RESULTS: The overall response rate was 26.4% (25.2% PC; 27.7% NC). Mean age of the PC patients was lower compared to the NC patients (47 vs 52, p<0.001). PC patients were more likely to have taken an herbal or dietary supplement (56.9% vs 45.2%, p=0.013). The NC patients took more traditional medications than the PC patients (5.4 vs 1.6, p<0.001). More PC patients took echinacea compared to the NC patients (25.7% vs 12.0%, p=0.009). The most common supplements taken by the PC patients were echinacea (25.7%), green tea (19.9%) and chamomile (13.7%). The most common supplements taken by the NC patients were chamomile (13.6%), echinacea (12.0%) and garlic (12.0%).
CONCLUSIONS: Use of herbal and dietary supplements among PC patients was higher than NC patients. The substantial use of herbal and dietary supplements in both primary and nephrology clinics support the need for health care providers to document and monitor use of these products.

104. Use of alternative pharmacotherapy by consumers in community pharmacies in a metropolitan city. *Fraidy N. Maltz, Pharm.D.,* Judy W.M. Cheng, Pharm.D., BCPS, Harold L. Kirschenbaum, M.S., Pharm.D., Vitalina Rozenfeld, Pharm.D., Stanley Feifer, M.S.; Long Island University, Brooklyn, NY.

PURPOSE: This survey was designed to (1) determine demographics effect on alternative pharmacotherapy (AP) use (2) assess patients' knowledge and beliefs of AP, (3) determine number of patients who disclose AP usage to health care providers, and (4) determine most common AP used in the New York metropolitan area.
METHODS: 192 consumers (106 AP users and 86 nonusers) were invited to complete the survey between January and March 2001 at 29 community pharmacies.
RESULTS: Demographic data were not different between groups. Diseases more frequently associated with users were hypercholesterolemia (10.4% vs 1.2% non-users; p=0.004), arthritis (10.4% vs 2.3% non-users; p=0.02), and depression (5.7% vs 0% non-users; p=0.007). Top 10 AP used were multivitamins (30%), vitamin C (26%), vitamin E (18%), echinacea (15.1%), garlic (15.1%), calcium (14.2%), ginkgo (14.2%), ginseng (10.4%), vitamin B-complex (9.4%), glucosamine (7.5%). Forty-two percent used AP due to friends' recommendation. Twenty-six percent consulted physicians and 30% consulted pharmacists before using AP. Ninety percent of users knew the indications but only 20.8% and 2.8% were aware of side effects and drug interactions respectively. Compared with nonusers, more users (47.2% vs 26.7%; p=0.004) believed AP to be effective. Similar percentage of users and nonusers believed AP is safe (26.4% vs 22.1%; p=0.478).
CONCLUSIONS: Patients with chronic diseases (hypercholesterolemia, arthritis, and depression) were more likely to use AP. Few patients disclose their AP usage to health-care providers. Consumers who used AP know the indications, but were less aware of adverse effects/ drug interactions. Further patient education regarding AP used is necessary.

105. Use of complementary and alternative medicine in the literature: who is missing and why. *Patrick G. Clay, Pharm.D.,* Kevin A. Clauson, Pharm.D.; University of Missouri at Kansas City, Kansas City, MO.

PURPOSE: To review all published data on the use of complementary and alternative medicines (CAM) in protected, low income and minority populations. To assess the applicability of traditional CAM use studies to these populations. To evaluate reasons for the discrepancy and methods to be implemented in future studies so that much needed data is available.
METHODS: Primary articles were identified by Medline and EMBASE searches. All of the articles identified from the data sources were evaluated and all information deemed relevant was included in this review.
RESULTS: For the majority of studies in the literature offering data concerning the use of CAM in protected, low income and minority patients, the data is skewed to underreport the occurrence. The limited studies currently available that specifically targeted low income and minority

populations show an alarmingly higher rate of use of CAM than previously reported. Studies specifically assessing the use of CAM in protected populations show rates substantially higher than the national average. The potential for conventional and alternative medicine interaction as well as untoward outcomes is greater as clinicians in these populations have not been made aware of the incidence of use in these populations.
CONCLUSIONS: CAM use in protected, low income and minority patients is 1.2 to 2 times that seen in the national population. The previously characterized typical CAM patient should be reassessed in light of study design flaws and assessment techniques.

HIV/AIDS

106. Pharmacokinetics of enteric-coated didanosine in HIV-infected pediatric patients. *Jennifer R. King, Pharm.D.,* Sharon Nachman, M.D., Ram Yogev, M.D., Grace Aldrovandi, M.D., Bharat Damle, Ph.D., Janice Hodge, R.N., Andrew Wiznia, M.D., Edward P. Acosta, Pharm.D. for the Pediatric AIDS Clinical Trials Group 403 Team; University of Alabama at Birmingham, Birmingham, AL; SUNY Stony Brook, Stony Brook, NY; Children's Memorial Hospital, Chicago, IL; Bristol-Myers Squibb, Princeton, NJ; Frontier Science and Technology, Amherst, NY; Jacobi Medical Center, Brooklyn, NY.

PURPOSE: The pharmacokinetics (PK) of enteric-coated didanosine (ddI EC) have not previously been evaluated in pediatric patients. The purpose of this study was to evaluate ddI absorption and disposition from the EC formulation in HIV-infected children.
METHODS: Eight children received a single ddI EC dose of 240 mg/m^2. Subjects received standard ddI (240 mg/m^2 QD) between 12-52 weeks prior to the single-dose EC study. Blood samples for ddI determination in plasma were collected at pre-dose, 0.5, 1, 2, 4, 8 and 12 hours post-dose and quantitated using a validated radioimmunoassay. Primary parameters (AUC_∞, C_{max} and T_{max}) were determined using noncompartmental methods. Regression was used to determine half-life ($t_{1/2}$). Measured values below the limit of quantitation (BLQ, 3 ng/ml) were considered zero.
RESULTS: PK data from one subject was not evaluable. The mean ± SD (n=7) dose, age and weight were 244 ± 28 mg/m^2, 7.7 ± 2.7 years, and 29.8 ± 16.4 kg, respectively. The AUC_∞, C_{max}, and T_{max} were 2591 ± 843 ng.h/ml, 900 ± 507 ng/ml, and 3.3 ± 2.4 hours, respectively. $T_{1/2}$ was 1.3 ± 0.6 hours and C12H was 15 ± 24 ng/ml. All pre-dose ddI plasma concentrations were BLQ, and 3 out of 7 (43%) of C12H values were BLQ.
CONCLUSIONS: The ddI EC formulation exhibits a slower rate but similar extent of absorption compared with buffered formulations in children. The ddI EC C_{max} was about 60% of that for the ddI tablet and T_{max} was prolonged approximately 5-fold. AUC_∞, oral clearance, and $t_{1/2}$ are similar to previously reported PK data. This formulation will allow more convenient dosing regimens for children.

107. Efficacy and safety of pravastatin in protease inhibitor-related hyperlipidemia (PIH). *Michelle R. Lowe, Pharm.D.,* Susan K. Chuck, Pharm.D., BCPS, Scott R. Penzak, Pharm.D.; Grady Health System; Mercer University, Atlanta, GA.

PURPOSE: Pravastatin is recommended by ACTG guidelines for PIH treatment based on drug interaction data, however, limited efficacy and safety data exists.
METHODS: Prospective analysis of pravastatin in PIH using NCEP II guidelines was conducted. Pravastatin was dosed for 12 weeks; 20 mg/d increased to 40 mg/d at week 4 as needed to achieve NCEP goal. Baseline, week 4, and week 12 fasting lipid profile, transaminases, CD4 count, HIV RNA and toxicity symptoms (muscle weakness, tenderness, pain) were monitored for efficacy and safety. Student's t-test was used to compare baseline and week 12 differences.
RESULTS: Seventeen patients (44 ± 4 years, 82% male). Twelve patients were titrated to 40 mg/d. High triglycerides (TG) resulted in LDL calculation for 9 and 13 patients at baseline and week 12. Baseline and week 12 data (mg/dl; mean ± SD) for LDL were 216 ± 44 and 158 ± 14 (p=0.003); total cholesterol 327 ± 74 and 257 ± 70 (p=0.000005); HDL 41 ± 10 and 43 ± 10 (p=0.36); and TG 607 ± 625 and 526 ± 689 (p=0.22). Inter-patient change (mean% and mean absolute) for LDL -25%, -58 mg/dl; total cholesterol -21%, -70 mg/dl; HDL +7%, +6 mg/dl; and TG -20%, -191 mg/dl. Excluding an outlier with an 80% TG increase, mean% change was -26% (p=0.009). 4/8 patients without calculated baseline LDL (TG>400) achieved LDL goal at week 12. Half (6/13) of evaluable patients (TG<400) achieved LDL goal at week 12. One patient reported myalgia not attributable to therapy (normal CPK). No significant difference in the mean CD4 count, HIV RNA, and transaminases were noted at week 12.
CONCLUSION: Pravastatin therapy is safe and provides clinically and statistically significant reductions in LDL, total cholesterol and TG with LDL goals achieved in half of patients.

108E. Disparity in highly active antiretroviral medication (HAART) regimen initiation and maintenance in African-American patients in a medically indigent population. *Patrick G. Clay, Pharm.D.,* J.R. Boyd, A. Lyman; University of Missouri at Kansas City, Kansas City, MO; Truman Medical Center, Kansas City, MO; Kaiser Permanente, Denver, CO.

PURPOSE: Our clinic has recently performed a quality assurance study to determine if a difference exists in either rate of therapy initiation or response to HAART.
METHODS: 389 patient charts was conducted to determine if a difference existed in care given or response rates to HAART between African-Americans (group 1) and non-African Americans (Caucasians, 92%, group 2). The data was collected to compare percentage of patients in each group on or offered HAART and if on therapy, response rate and magnitude were compared. If not on or offered HAART, the reasons were collected and ranked.
RESULTS: Of group 1 (n=89) and group 2 (n=300), patients on therapy for a mean of 522 days (± 49, 95% CI), 64% and 77% were prescribed at least one HAART regimen (p=0.02). Only 68% versus 89% of those had virologic response data in group 1 and group 2, respectively (p<0.001). Viral load decrease of evaluable patients was 1.83 and 1.81 log10, respectively (p=0.3). Group 1 and group 2 proportions of: responders (77% vs 80%), viral loads <400 (77% vs 76%) and viral loads <50 (54% vs 51%) were not different. Of group 1 not on therapy at the time of review, reasons for either not being offered, declining or discontinuing therapy were collected and ranked.
CONCLUSION: A significant difference was found in rate of HAART initiation and number of evaluable patients. No difference was found in response to therapy between groups.
Presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Toronto, Ontario, Canada, September 19, 2000.

109E. Effect of methadone (M) or LAAM (L) on nelfinavir pharmacokinetics. *Patrick F. Smith, Pharm.D.,* Brent M. Booker, Pharm.D., Robin DiFrancesco, Gene D. Morse, Pharm.D., Peter F. Cottone, Mary K. Murphy, Elinore McCance-Katz, M.D.; University at Buffalo, Buffalo, NY; Roswell Park Cancer Institute, Buffalo, NY; Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY.

PURPOSE: NFV is often co-administered with M or L. M inhibits CYP450, but its effects on NFV and M8 have not been prospectively evaluated. Our purpose was to evaluate the pharmacokinetics (PK) of NFV and M8 in combination with M or L.
METHODS: In a non-crossover design, healthy, non-HIV infected volunteers either maintained on stable doses of M (40-120 mg/d; n=16) or L (50-140 mg twice weekly, 65-190 mg once weekly; n=10) for 4 weeks or non-opioid dependent controls (CTL; n=15) received NFV (1250 mg BID) for 5 days followed by steady-state PK evaluation. PK samples were collected over 24 h and assayed (HPLC) for NFV and M8 at 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, and 24 h. PK parameters determined by standard non-compartmental methods were compared to CTL by non-parametric ANOVA.

RESULTS: Gmean (SD) PK parameters were:

	Tmax (h)	Cmax (uM)	T1/2 (h)	Vd (L)	$AUC_{0\text{-}12}$ (um/ml•h)
NFV-Ctrl	2.0 (0.4)	8.0 (1.3)	4.4 (0.5)	232 (51)	52.2 (9.9)
NFV-LAAM	2.9 (0.5)	7.1 (0.7)	5.9 (0.6)	305 (39)	53.3 (5.6)
NFV-METH	1.8 (0.6)	7.7 (1.0)	6.3 (2.3)	291 (283)	59.4 (8.6)
M8-Ctrl	3.3 (0.4)	3.0 (0.4)	4.0 (0.7)	615 (175)	18.0 (2.8)
M8-LAAM	4.5 (0.4)	4.0 (0.5)	5.0 (0.5)	510 (69)	26.8 (3.3)^
M8-METH	2.4 (0.6)	1.4 (0.3)*	4.6 (1.1)	1074 (332)	9.5 (2.5)*

*p<0.05; ^p=0.07 when compared to control

When compared to CTL, geometric mean NFV 12-hr troughs were higher (3.3 vs 1.2 uM, p<0.05) in the M group, and did not differ with L. The metabolic AUC ratio (M8:NFV) for CTL was 0.38, and was significantly higher with L (0.51), and lower with M (0.24), both p<0.05.
CONCLUSIONS: NFV exposure tended to be higher, and M8 significantly lower when co-administered with M, while the opposite trend was evident with L. M effects may be consistent with inhibition of the conversion of NFV to M8, while L may to increase the conversion rate of NVF to M8.
Presented at the 109th Annual Convention of the American Psychological Association, San Francisco, CA, August 24-28, 2001.

110E. Effects of once daily saquinavir/mini-dose ritonavir on the pharmacokinetics of methadone isomers. *Mark J. Shelton, Pharm.D.,* Denise Cloen, RN, Charles Berenson, M.D., Andrew Esch, M.D., Keith Wagner, Pharm.D., Robin DeFrancesco, Ross G. Hewitt, M.D.; University at Buffalo; VA Western New York Healthcare Systems; and Sister's Health Care Systems, Buffalo, NY.

PURPOSE: Both ritonavir (500 mg BID) and ritonavir/saquinavir (400 mg BID each) reduce methadone pharmacokinetic (PK) exposure. However, saquinavir in combination with mini-dose ritonavir (given once daily) has not been evaluated. Once daily antiretroviral regimens may simplify therapy for patients in methadone maintenance programs.
METHODS: HIV-negative volunteers on stable methadone were evaluated before (PK Day 0) and after (PK Day 14) directly-observed, saquinavir/ritonavir therapy (1600 mg/100 mg, respectively, given once daily for 14 days concurrently with methadone doses and a meal.) On each PK day, blood was

sampled at 0, 1, 2, 3, 4, 6, 8, 10, and 24 hours after dosing. R-methadone (active isomer) and S-methadone plasma concentrations were determined using validated HPLC assays. Noncompartmental PK parameters (C_{max}, $AUC_{0\text{-}24h}$, C_{min}) were determined, along with geometric mean ratios (GMR) and 90% confidence intervals (CI) of the PK Day 14/PK Day 0 ratio for each PK parameter.

RESULTS: 12 subjects receiving methadone doses from 35-100 mg were enrolled: 7 females/5 males, including 7/12 with hepatitis C infection. All subjects tolerated the regimen and did not require methadone dose changes during the study. GMRs for PK parameters, upper 90% CI (U90%CI), and lower 90% CI (L90%CI) are:

	R-methadone			S-methadone		
	C_{max}	$AUC_{0\text{-}24h}$	C_{min}	C_{max}	$AUC_{0\text{-}24h}$	C_{min}
GMR:	1.03	1.03	1.04	0.93	0.91	0.87
U90%CI	0.91	0.91	0.87	0.84	0.82	0.69
L90%CI	1.16	1.16	1.25	1.04	1.01	1.10

Gender and hepatitis C infection did not impact GMR for any parameter.

CONCLUSIONS: Once daily saquinavir/mini-dose ritonavir is well tolerated and does not affect pharmacokinetic exposure to R-methadone.
Presented at the 2nd International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, The Netherlands, April 2-4, 2001.

111. An evaluation of cardiovascular risk monitoring and treatment in HIV/AIDS patients. *Omar Badawi, Pharm.D.,* Mahtab Jafari, Pharm.D., Reza Movahed, M.D., Leila Bagkhani; University of California, Irvine Medical Center, Orange, CA.

PURPOSE: This study documented the monitoring and treatment patterns of CAD risk factors in the HIV+ population at a University hospital setting. Secondary objectives documented the incidence of CAD and dyslipidemia in a sample of HIV+ patients in a University hospital.
METHODS: Medical records of 202 HIV+ patients visiting a university teaching hospital between July 1999 and September 2000 were reviewed. Patient demographics, years of HIV diagnosis, CAD risk factors, prior medical history, viral load, CD4, lipid panel and LFTs were documented.
RESULTS: Complete risk factor assessment was documented in 20.3% of patients. Lipid panels were not obtained in 35% of patients. Five out of seven patients with secondary prevention goals for CAD with LDL > 130 without contraindications to therapy were not on any lipid lowering medication. 47% of patients on protease inhibitors had no triglyceride levels obtained in the past 12 months. Incidence of CAD was 3.5% with the incidence of dyslipidemia being consistent with published data in this population.
CONCLUSION: With advances in the treatment of HIV, patients are beginning to manifest other disease states that were not previously encountered in this population. This study demonstrates the need to modify our approach to identifying and managing HIV+ patients at risk for CAD.

112. Tolerability of efavirenz in patients with a history of mental health disorder or substance abuse. *Kathryn E. DeSilva, Pharm.D.,* Tiffany D. Flaherty, Pharm.D., Jodie L. Guest, Ph.D., M.P.H., Barbara J. Marston, M.D., David Rimland, M.D.; Atlanta Veterans Affairs Medical Center; Emory University School of Medicine, Atlanta, GA.

PURPOSE: To determine whether patients with a history of mental health disorder (MHD) and/or substance abuse (SA) tolerate efavirenz (EFV) any differently than those without such a history.
METHODS: All patients who were issued prescriptions for EFV through the Atlanta VAMC were identified. Patients were classified into one of four groups according to medical history: MHD, SA, both, and neither. Retrospective chart review was performed; data collected included number of patients developing central nervous system (CNS) adverse effects and time to onset, time on EFV, and EFV discontinuation (D/C) rates and reasons. Univariate analysis was performed using SAS.
RESULTS: A total of 220 patients were included; 23% had a history of MHD, 25% SA, 17% both, and 36% neither. Early and late CNS effects occurred in 61% and 21%, respectively, and did not differ according to group. Twenty-eight stopped EFV due to CNS effects, 27 of whom had experienced early CNS effects (p=0.001). D/C was not associated with patient group (p=0.445). D/C rate due to CNS effects was significantly greater in our patient population than in product literature (RR=4.2, 95% CI=2.22-8.27; p<0.0001).
CONCLUSIONS: There was no statistically significant increased risk for early CNS effects in patients with MHD and SA. Patients with late CNS effects and those who D/C due to CNS effects were more likely to have had early CNS effects. Our higher incidence rate of CNS effects and D/C rate may better reflect "real world" experiences.

Infectious Diseases

113. Comparison of in vitro activity of piperacillin/tazobactam, cefepime, imipenem, and meropenem against extended-spectrum β-lactamase (ESBL) and non-ESBL-producing *K. pneumoniae* by time-kill methodology. *David S. Burgess, Pharm.D.*; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX.

PURPOSE: *K. pneumoniae* have become more resistant to antibiotics by the production of extended-spectrum β-lactamase (ESBL). ESBLs differ from classic β-lactamases by only 1 or 2 amino acids. However, the detection of organisms producing ESBL is difficult and the optimal treatment of these organisms is unknown. This study compared the in vitro activity of several β-lactams against ESBL and non-ESBL *K. pneumoniae* by time-kill methodology.
METHODS: MICs and time-kill curves (using achievable serum concentrations) were performed against 8 *K. pneumoniae* (4 non-ESBL and 4 ESBL) for piperacillin/tazobactam (Pip/Tazo, 40/5 µg/ml), cefepime (CFP, 20 µg/ml), imipenem (IMI, 4 µg/ml), and meropenem (MERO, 4 µg/ml). The ETEST ESBL strip containing ceftazidime ± clavulanate confirmed the presence of ESBL. Samples were withdrawn at 7 predetermined timepoints over 24 h and plated on TSA plates. After 24 h of incubation at 35°C, colony counts were determined. All organisms surviving at 24 hr had MICs performed to determine whether resistance had developed.
RESULTS: MICs were: Pip/Tazo 4-8 µg/ml (ESBL and non-ESBL), CFP 1-2 µg/ml (ESBL) and 0.06-0.125 µg/ml (non-ESBL), IMI 0.125-0.25 µg/ml (ESBL and non-ESBL), and MERO 0.03-0.06 µg/ml (ESBL and non-ESBL). Each antibiotic demonstrated 99.9% killing and no regrowth against all of the non-ESBL isolates. IMI, MERO, and CFP demonstrated the same activity against each ESBL isolate as non-ESBL isolate. However, Pip/Tazo demonstrated 99.9% killing against only 1 ESBL isolate. Furthermore, all ESBL isolates demonstrated significant regrowth and being highly resistant to Pip/Tazo (MICs ≥ 256 µg/ml).
CONCLUSIONS: Cefepime, imipenem, and meropenem displayed significantly more in vitro killing against ESBL *K. pneumoniae* than piperacillin/tazobactam. The clinical relevance of these findings needs to be further evaluated in clinical trials.

114. Gene expression profiling of amphotericin B exposure in human peripheral blood mononuclear cells. *P. David Rogers, Pharm.D., M.S.,* John D. Cleary, Pharm.D., Donna C. Sullivan, Ph.D., Stanley W. Chapman, M.D.; University of Mississippi, Jackson, MS.

PURPOSE: Amphotericin B (AmB) has been shown to induce the expression of genes encoding immunomodulatory proteins in human monocytic cell lines. Our purpose was to identify genes that are differentially expressed in hPBMCs in vitro in response to AmB.
METHODS: hPBMCs were isolated from the blood of 5 healthy volunteers and cultured in supplemented medium in the presence or absence of 5 µg/ml AmB for 2 hours. Total RNA was extracted and $^{[33]}$P dCTP-labeled cDNA probes were prepared by reverse transcription. Probes were hybridized overnight with Res. Genetics GF211 Named Genes Human Genefilter cDNA arrays at 42°C. Washed arrays were exposed to a phosphor screen for 72 hours and imaged. Experiments were performed in duplicate. Data were analyzed using Res. Genetics Pathways 3.0 software. A ≥ two-fold difference in expression was considered significant.
RESULTS: Of 4,324 genes evaluated, 17 genes were up-regulated and 14 genes were down-regulated in hPBMCs after exposure to AmB for 2 hours. Up-regulated genes included those encoding MIP-1α, MIP-1β, IL-1α, IL-8, IL-1Ra, cyclophilin, TNF receptor-associated factor 1, and COX2. Down-regulated genes included TYRO protein tyrosine kinase binding protein, interferon γ-inducible protein 30 and MCP-1.
CONCLUSION: AmB alters the *in vitro* expression of genes encoding immunomodulatory proteins in hPBMCs. Increased production of chemoattractant chemokines, proinflammatory cytokines, and prostaglandins in response to AmB may enhance the immune response to fungal pathogens, but may also be involved in the toxicity associated with this drug.

115. Genome-wide evaluation of differential gene expression in response to sub-inhibitory concentrations of amphotericin B in *Saccharomyces cerevisiae*. *P. David Rogers, Pharm.D., M.S.,* Margaret M. Pearson, Pharm.D., M.S., Katherine S. Barker, Ph.D., John D. Cleary, Pharm.D., V. Evette Porter, B.S., Donna C. Sullivan, Ph.D., Stanley W. Chapman M.D.; University of Mississippi, Jackson, MS.

PURPOSE: Amphotericin B (AmB) is believed to act by binding to ergosterol in the fungal cell membrane and causing leakage of intracellular contents. AmB alters the expression of many genes in human cells. The purpose of this study was to identify genes that are differentially expressed in *Saccharomyces cerevisiae* in response to sub-inhibitory concentrations of AmB.
METHODS: cDNA array analysis was used to perform a complete genome comparison of mRNA populations from *S. cerevisiae* grown in the presence or absence of AmB at 0.5 X MIC for 90 minutes. Isolates were grown in brain heart infusion broth at 37°C in a shaking incubator. Total RNA was extracted and $^{[33]}$P dCTP-labeled cDNA probes were prepared and hybridized overnight with Research Genetics GF100 Yeast Genefilter cDNA arrays at 42°C. Imaging was performed with a phosphorimager. Experiments were performed in duplicate. Data were analyzed using the Research Genetics Pathways 3.0 software.
RESULTS: Of 6,144 genes evaluated, 54 were up-regulated and 45 genes were down-regulated after exposure to AmB. Up-regulated genes included the transcription factor *GAT1*, POL II transcription genes including *SKO1*, *NHP6B*, *SON1*, and *TFC3*, and the cell wall maintenance gene *KRE5*. Those

down-regulated included carbohydrate metabolism genes *ENO2*, *RHR2*, *TDH1*, *TDH2*, *TDH3*, and *GPM1* as well genes involved in protein synthesis.
CONCLUSION: AmB alters expression of genes involved in POL II transcription, carbohydrate metabolism and protein synthesis independent of its effect on cell growth. Such effects may represent previously undescribed mechanisms of action of this antifungal agent.

116. 5-Fluorocytosine-induced differential gene expression in human monocytic cells. *Margaret Pearson, Pharm.D.,* J.D. Cleary, Pharm.D., P.D. Rogers, Pharm.D., S.W. Chapman, M.D. University of Mississippi, Jackson, MS.

PURPOSE: Toxicity and activity of 5-fluorocytosine (5-FC) activity may be predictable based on changes in gene expression profiles. The purpose of this study was to identify genes that are differentially expressed in human monocytic (THP-1) cells *in vitro* in response to 5-FC.
METHODS: THP-1 cells (3.0×10^7 cells) were exposed for 6 hours to 5-FC or media. Total RNA was isolated from cells using the TRIazole reagent. cDNA was synthesized using anchoring primers then amplified in the presence of $^{[33]}$P dCTP. Complimentary DNA were hybridized to a human gene array containing >4300 known genes. The identity of specific genes with altered regulation (> 2 fold) was performed by using variable intensity analysis between the two exposures. Significant genes are validated using RT-PCR with unique primers.
RESULTS: Twenty-eight up- and 134 down-regulated genes were considered unique to antifungal exposure. Six genes involved in blood coagulation, hemostasis, or heme biosynthesis were down-regulated (*PABPC4*, *THBD*, *ARHGDIA*, *NFE2*, *GSS* and *CYB5*). One gene involved in vitamin B12 transport was down-regulated (*TCN2*). No genes involved in hemostasis or hematopoiesis were up-regulated.
CONCLUSIONS: This study has identified a number of monocytic mRNAs representing altered gene regulation associated with 5-FC. Further investigation may elucidate novel pathways involved in human toxicity and activity against yeast.

117. Quinupristin/dalfopristin: risk factors for arthralgias and myalgias. *Peggy L. Carver,* Heather Vandenbussche, Carol A. Kauffman, Emily Whang, Preeti Malani; University of Michigan; University of Michigan Health System; Veterans Administration Medical Center, Ann Arbor, MI.

BACKGROUND: Quinupristin/Dalfopristin (Q/D) administration has been associated with a high incidence of arthralgias and myalgias (AM). Risk factors for this adverse event are unclear but may be related to the presence of liver disease.
METHODS: All available medical records for 68 patients who received Q/D from February 1998 through September 2000. Risk factors evaluated included the presence of chronic liver or renal disease or dialysis, hematologic malignancy, major surgery, transplantation, ICU stay, mechanical ventilation, or the use of medications likely to interact with Q/D via cytochrome P450.
RESULTS: Of 68 patients evaluated, 18 patients were unassessable due to their underlying clinical condition (coma, heavy sedation). Of the remaining 50 patients, 25 (50%) experienced AM. Significant ($P<0.05$) risk factors for AM included the presence of chronic liver (but not renal) disease, receipt of liver (but not bone marrow) transplants, major surgery or ICU stay, but not mechanical ventilation. Patients who received mycophenolate, cyclosporine (but not tacrolimus), steroids, or fluconazole were also at higher risk for AM. Although Q/D is an inhibitor of CYP3A4, elevation of CYP3A4 substrates (e.g., cyclosporine) was not consistently observed.
CONCLUSION: AM were experienced by 50% of patients; however, in many patients likely to receive Q/D the presence of AM is not assessable due to underlying disease states. Specific patient populations may be at higher risk for AM due to underlying disease states and/or concomitant medication use.

118. Evaluation of the antimicrobial properties of the *Myrothamnus flabellifolius* essential oil against a variety of fungal and bacterial pathogens using time-kill methods. *Michael E. Klepser, Pharm.D.,* Sandy van Vuuren, Douglas Keele, Ellen Roling, Alvaro M. Viljoen, Ph.D.; Ferris State University, Big Rapids, MI; University of the Witwatersrand, Park Town, South Africa; University of Iowa, Iowa City, IA.

PURPOSE: *Myrothamnus flabellifolius* is a woody shrub employed for the treatment a variety of ailments including bacterial and fungal infections. We sought to evaluate the antimicrobial properties of essential oil derived from this plant against fungal and bacterial pathogens.
METHODS: Plant material was hydro-distilled to obtain the oil. Samples were analyzed using GC and GC-MS to characterize and ensure uniform oil composition. Three *Staphylococcus aureus* (1 MSSA and 2 MRSA), two *Candida albicans*, and one *Pseudomonas aeruginosa* were selected for testing. The minimum inhibitory percentage (MIP) of the oil was determined for each isolate in appropriate media. Time-kill studies were performed in duplicate with each isolate using oil concentrations ranging from 0.0625-1.0%.
RESULTS: Eighty-five compounds were identified in the oil. The major constituents were trans-pinocarveol (19.57%) and pinocarvone (11.13%). All isolates were inhibited at oil percentages ranging from 0.125-0.5%. Against *C. albicans*, the oil exhibited fungicidal activity at concentrations ≥ MIP. Against the staphylococci, the oil was bacteriostatic at the MIP; however, at higher concentrations, the rate and extent of killing produced improved in a concentration-dependent manner. Against the isolate of *P. aeruginosa*, initial rapid reduction in viable counts was noted with concentrations > MIP; however, significant regrowth was noted by the end of the study period.
CONCLUSIONS: The essential oil derived from *Myrothamnus flabellifolius* exhibits rapidly cidal activity at relatively low oil concentrations against *C. albicans* (0.125%) and *S. aureus* (0.5%). Our findings are exciting and encourage further in vitro and in vivo investigation of the antimicrobial properties of this oil.

119. Decreasing susceptibility (S) to fluoroquinolones (FQ) over time: differences in geographic areas. *Kevin A. Enzweiler, Pharm.D.,* Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: Bacterial susceptibility to FQ continues to decrease over time but may vary from one region of the world to another.
METHODS: We assessed S trends of 20 bacterial pathogens to 6 FQ, ciprofloxacin (C), gatifloxacin (GA), gemifloxacin (GE), levofloxacin (L), moxifloxacin (M), and BMS-284756, for 1983-2001 in North America (NA), Asia (A), and Europe (E) using a database of studies published during that time period. Using data from at least 3 studies over at least 2 years, linear regression of log MIC_{90} vs time was performed for each organism/drug combination. Those relationships with $R^2 \geq 0.7$, indicating a mathematically strong relationship, were further evaluated.
RESULTS: Of 360 potential drug/organisms relationships, 90 met our criteria (29, 26 and 35 for NA, A and E, respectively). Positive (+) slopes (n=47) from the analysis, indicating increasing MIC (decreasing susceptibility) over time, were detected in 59, 46 and 51% of possible instances of NA, A and E. GE and *E. cloacae* were most commonly involved in relationship with + slopes while L and *S. marcescens* were most commonly involved in those with negative (-) slopes. In a subset of data reflecting steepest + slopes (≥0.9; n=14), 36 and 64% occurred in A and E, respectively. GA and M accounted for most of the subset of steepest slopes (64% of total). Of the 7 Gram + and 13 Gram - organisms evaluated, the steepest + slopes were most often associated with the genus enterobacter (36% of total).
CONCLUSIONS: Decreasing susceptibility to the FQ was detected in each of 3 geographic areas although the most dramatic changes (steepest slopes) were confined to E and A. Unlike the results of our previous analyses, + slope relationships were not related to years of use of FQ and were evenly distributed across all geographic areas. Of note, this manner of quantitative analysis of MIC data over time may reflect changes in S prior to methods using categorical breakpoints.

120E. Monte Carlo analysis of levofloxacin (L) and gatifloxacin (G) pharmacodynamics using expected dosing in a patient population with varying degrees of renal function (RF) and 4,738 recent clinical isolates of *Streptococcus pneumoniae* (SP). Roger L. White, Pharm.D., *Kevin A. Enzweiler, Pharm.D.,* Lawrence V. Friedrich, Pharm.D., Kurt R. Lorenz, Pharm.D., Eberhard O. Voit, Ph.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC; Bristol-Myers Squibb, Princeton, NJ.

BACKGROUND: Monte Carlo simulation may allow a better assessment of the expected pharmacodynamics (PD) of an antimicrobial in a population of patients than methods that use single point estimates of drug exposure (AUC) and potency (MIC). With fluoroquinolones, minimal AUC 24 hr/MIC ratios of at least 30 appear to be associated with a good outcome for SP. Higher AUC/MIC ratios may be optimal.
METHODS: E test MIC testing of L and G was performed on 4,738 isolates of SP collected between 1/1/99 and 8/7/00 from 101 institutions across the USA. We utilized our institution's patient population admitted during one calendar year which theoretically represents a CrCl (RF) distribution typical of a tertiary care hospital (mean ± SD: 55 ± 30 ml/min) and determined PD for IV L and G. Free (unbound) AUCs were derived for a 70 kg patient from manufacturers' recommended dose/interval for varying RF and published CrCl vs drug clearance relationships. Monte Carlo analysis was performed using 1,000 patient simulations for the RF population and each MIC distribution. The probabilities of achieving AUC 24 hr/MIC ratios of at least 30 and 60 were assessed.
RESULTS: MIC_{50}, and MIC_{90} (mg/L) were 1.0 and 1.5 for L and 0.25 and 0.38 for G, respectively (range for both drugs: 0.016->32). The probabilities of achieving an AUC/MIC ratio of at least 30 for L and G were 85 and 99%, respectively. The probabilities of achieving an AUC/MIC ratio of at least 60 for L and G were 29 and 90%, respectively.
CONCLUSION: The probability of achieving a desired ratio of at least 30 is very high for both L and G in our RF population. However, the probability of achieving higher ratios (60) is much greater with G.
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121. Comparative carbapenem (CP) pharmacodynamics (PD) against common Gram-positive and Gram-negative organisms. *Kevin A. Enzweiler, Pharm.D.,* John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: The PD parameter associated with CP efficacy is percentage of the dosing interval the serum concentration remains above the MIC (%T > MIC). Increased interest in both marketed and experimental CPs warrants a PD comparison of these drugs.
METHODS: Pharmacokinetic (PK) parameters obtained from peer-reviewed publications in normal volunteers (NV) were used to simulate unbound serum concentration-time profiles (70 kg adult) for IV or PO imipenem (I), meropenem (M), ertapenem (E), faropenem (F), and DU6681a (D). Variability in Cl was addressed with Cl_t vs CrCl regression. MIC_{50} and MIC_{90} values were obtained from N. American (I, M, E) or Asian (F, D) studies published from 1999-2001 for 2 Gram (+) and 7 Gram (-) aerobes, and *B. fragilis* (~11,100 drug/isolate pairs). Weighted geometric mean MICs were used for subsequent PD calculations. Using manufacturer-recommended and/or investigational regimens, simulations were performed at CrCl of 100, 75, 50, and 25 ml/min (66 regimens). The same dosing regimens/PK values were used for all levels of renal function for F and D. Patient (pt) PK profiles were simulated with M and I as above, but used Vss from patient PK studies. %T > MIC ≥ 25 and 50 was considered acceptable (accept.) and optimal, respectively, for all bacteria.
RESULTS: Over the studied CrCl range, for NV, the %T > MIC (% accept.) rank order was M, I > E > F, D for both MIC_{50} and MIC_{90}. M and I differed only with *P. aeruginosa* (M=100% I=75% accept.). With M 500 mg Q8H, *P. aeruginosa* % accept. =50%. Other organism coverage was similar. With patient PK data, %T > MIC_{90} (% accept.) was the same as with NV for M and differed only with *P. aeruginosa* for I (patient=83%, NV=75%).
CONCLUSION: M and I, which differed only with *P. aeruginosa,* exhibited more favorable PD profiles in these simulations than the other CPs.

122E. Assessment of the potential for city-wide antibiograms: differences in in vitro activity against *Streptococcus pneumoniae* within major metropolitan areas (MA) in the United States. Roger L. White, Pharm.D., Lawrence V. Friedrich, Pharm.D., *Kevin A. Enzweiler, Pharm.D.,* Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., David J. Wagner, Pharm.D.; Medical University of South Carolina, Charleston, SC; Bristol-Myers Squibb, Princeton, NJ.

BACKGROUND: Although antibiograms are usually constructed in individual hospitals, they may be combined to produce a single antibiogram for a MA, especially with increasing hospital mergers and use of centralized labs. An advantage of this is an improvement in statistical validity, thus producing a better representation of susceptibility patterns to be used in antibiotic selection.
METHODS: Using an E test MIC study of 2,100 isolates of *S. pneumoniae* from 47 institutions across the USA (16 cities, 13 states) for penicillin (P), levofloxacin (L), and gatifloxacin (G), we analyzed the potential utility of intra-city antibiograms. In each MA, at least two institutions with at least 20 isolates each were included. MIC_{50}/MIC_{90} and %S,I,R (NCCLS breakpoints) were calculated for each institution and each MA (combined institutions). Differences between individual institutions and the MA were assessed.
RESULTS: For individual institutions, the range of MIC_{50} and MIC_{90}s (mg/L) were: 0.02-1.5 and 0.09-6.0 for P, 0.32-1.5 and 0.75-2.0 for L, 0.13-0.38 and 0.19-0.75 for G. Minimum/maximum %R were 2/53 for P, 0/5 for L, 0/4 for G. Although the range of MICs of L and G was wide, most isolates were susceptible. However, P %R varied widely among MA (3-36%). MICs varied widely within a MA for L, G, and P, but deviation of %R for a given institution from the MA varied by only a maximum of 3% for L or G. However, %R for P varied from the MA by as much as 21%.
CONCLUSION: City-wide antibiograms could mask important differences in susceptibility patterns that should be considered in empiric prescribing of antimicrobials.
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123E. Comparative fluoroquinolone (FQ) pharmacodynamics (PD) against common Gram-positive and Gram-negative organisms over a range of creatinine clearance (CrCl). *Kevin A. Enzweiler, Pharm.D.,* Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: The PD parameters associated with FQ efficacy are area under concentration curve ($AUC_{0\text{-}24hr}$)/MIC and maximum serum concentration (C_{max})/MIC. Since many drugs are primarily renally eliminated, achievement of desired PD likely varies with renal function. Thus, PD analyses should incorporate assessments at various CrCl levels.
METHODS: Pharmacokinetic (PK) parameters obtained from peer-reviewed publications were used to simulate unbound serum concentration-time profiles (70kg adult) for IV and/or PO ciprofloxacin (C), gatifloxacin (G), levofloxacin (L), moxifloxacin (M), gemifloxacin (GM) and BMS-284756 (B). Using manufacturer-recommended and/or investigational non-UTI regimens, simulations were performed at CrCl of 100, 75, 50, and 25 ml/min and AUCs and C_{max} calculated. MIC_{90} values were obtained from N. American studies published from 1999-2001 for 2 Gram + and 8 Gram - organisms (~142,800 drug/organism pairs, mean 2380 organisms/drug). Weighted geometric mean MICs were used in PD calculations. AUC/MIC ≥30 and ≥100 were considered acceptable for Gram + and Gram - organisms, respectively. C_{max}/MIC ≥10 was considered acceptable for all.
RESULTS: Over the CrCl range, AUC/MICs increased by ~60% for L and G, while the increases were less with other FQs. Generally, increases did not alter the % of acceptable regimens. Against Gram positives, rank order for AUC/MIC was B (69-625) > M (101-204), G (65-320)> L (33-134), GM (28-174) > C (7-75). Against Gram-'s, rank order was G >C, L >B, GM, M. The rank order for C_{max}/MIC were similar.
CONCLUSION: Although PD indices varied with CrCl, the ability to achieve acceptable AUC/MIC and C_{max}/MIC ratios was independent of CrCl. Simulations using population PK parameters and MICs is useful in assessing differences in the PD profiles of FQs.
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124. Worldwide trends in carbapenem (CP) susceptibility (S) patterns, 1985-2000. *Kevin A. Enzweiler, Pharm.D.,* Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: Bacterial susceptibility to CPs continues to decrease over time, although rate and extent of change are largely unknown and may vary from one geographic area to another.
METHODS: We assessed S trends for imipenem (I), meropenem (M), faropenem (F), ertapenem, and DU-6681a from 1985 through 2000 in North America (NA), Asia (AS), and Europe (EU) using a database of studies published during that time period. Using ≥3 studies over at least 2 years, linear regression of log MIC_{90} vs time was performed for each organism/drug combination. Only those relationships with an $R^2 \geq 0.7$ were further evaluated. Median fold-change in MIC_{90} between consecutive years and the maximum/minimum MIC_{90} ratio (max/min ratio) over the study period were calculated for each organism/drug combination. The subset of data with the steepest positive (+) slopes (slope ≥0.9) were also analyzed.
RESULTS: Of 225 possible organism/drug relationships, 20% met our criteria ($R^2 \geq 0.7$). Of these, 22, 51, and 27% were from NA, AS and EU, respectively. Positive slopes, indicating increasing MICs (decreasing susceptibility over time), were detected in 20, 70 and 83% of possible instances for NA, AS and EU, respectively. Median fold increase in MIC_{90} in consecutive years and the max/min MIC_{90} ratio were 2 and 5, respectively. In the subset of data reflecting steepest slopes (n=17), 25, 75 and 100% of the slopes were + in NA, AS and EU, respectively. Of these, *S. pneumoniae* was involved in >50%. The rank order of CPs (in order of the likelihood of steepest + slopes) was F > M = I. Irrespective of which data set of + slopes (all data, $R^2 \geq 0.7$, or $R^2 \geq 0.7$ with steepest slopes) is considered, EU, *S. pneumoniae*, and F accounted for the largest percentages of + slopes of geographic regions, organisms, and drugs, respectively.
CONCLUSIONS: Using this database comprised of an extensive amount of published MIC data over time, increases in MIC_{90} were found for many clinically relevant CP/organism combinations in all geographic regions studied.

125. Relationship between infectious disease practices (IDP) and Gram-positive (GP) resistance in community hospitals throughout the United States (US). *Madhavi Manduru-Rao, Pharm.D.,* Katie J. Suda, Pharm.D., Kevin W. Garey, Pharm.D., Alisa E. Goetz, Pharm.D., Vikas Gupta, Pharm.D., BCPS, Larry H. Danziger, Pharm.D.; Owen Healthcare, Inc., Chicago, IL; University of Illinois at Chicago, Chicago, IL; Owen Healthcare, Inc., Houston, TX.

PURPOSE: Antimicrobial resistance to gram-positive bacteria has increased alarmingly in US hospitals. Data are scarce on the relationship of IDP and GP resistance, especially in community hospitals. The purpose of this study was to examine the relationship between IDP and resistance in GP bacteria.
METHODS: Community hospitals managed by Owen Healthcare provided antimicrobial susceptibility data, hospital demographics, and IDP from their institutions for the year 2000. Data were analyzed for susceptibility of *Staphylococcus aureus* vs methicillin (MRSA) and clindamycin (CL-SA), *Enterococcus faecium* vs ampicillin (amp-EF) and vancomycin (VREF), and *Streptococcus pneumoniae* vs penicillin (PCN-SP) by multivariate, stepwise, linear regression analysis. A p value < 0.05 was considered significant.
RESULTS: 56 hospitals with an average bed size of 175 ± 140 beds (mean ± SD) and 12 ± 12 ICU beds (13 teaching/43 non-teaching hospitals) provided data for the study. Infectious disease physicians and infection control committees were employed by 55% and 54% of hospitals, respectively. 95% of hospitals admitted patients from nursing homes. Hospitals with a higher number of ICU beds and teaching hospitals were more likely to have decreased susceptibility of CL-SA, VRE, and amp-EF ($p<0.05$). Hospitals that admitted from nursing homes or who did not have an ID physician were more likely to have decreased susceptibility of amp-EF and MRSA (ID physician only; $p<0.05$). Of interest, increasing bed size was associated with increasing susceptibility to CL-SA, VRE, and amp-EF.
CONCLUSION: Susceptibility patterns for GP organisms differed based on hospital demographics and IDP employed in community hospitals throughout the US.

126. Nationwide surveillance of antimicrobial resistance patterns in non-teaching, community hospitals for the year 2000. *Katie J. Suda, Pharm.D.,* Kevin W. Garey, Pharm.D., Madhavi Manduru-Rao, Pharm.D., Alisa E. Goetz, Pharm.D., Vikas Gupta, Pharm.D., BCPS, Larry H. Danziger, Pharm.D.; University of Illinois at Chicago, Chicago, IL; Owen Healthcare, Inc., Chicago, IL; Owen Healthcare, Inc., Houston, TX.

PURPOSE: The Center for Disease Control and Prevention has stressed the importance of collecting regional and national antibiotic resistance patterns. Although surveillance systems have been established primarily among large, teaching hospitals, data on susceptibility patterns specific to community hospitals is scarce. The purpose of this research was to report on an ongoing surveillance to determine pathogen frequency and antimicrobial susceptibility patterns from US community hospitals for the year 2000.
METHODS: Community, non-teaching hospitals within Owen Healthcare provided antibiotic susceptibility reports from the year 2000 along with hospital demographics. Only hospitals that used automatic susceptibility testing methods and were able to exclude duplicate isolates were included.
RESULTS: 114 of 300 hospitals responded of which 52 were eligible for analysis representing 121,527 bacterial isolates. Gram negative bacilli were most commonly isolated (66%) followed by gram positive cocci (33%). The most commonly isolated organisms were escherichia (29%), staphylococcus (21%), klebsiella (10%), enterococcus (10%), pseudomonas (8%), proteus (7%), enterobacter (4%), and streptococcus (2%). Nationwide, resistance was noted for methicillin-resistant *S. aureus* (MRSA; 39%), vancomycin-resistant *Enterococcus* (VRE; 7%) and VRE *faecium* (49%), ceftazidime-resistant *K. pneumoniae/E. coli* (5%/2%), *P. aeruginosa* resistant to levofloxacin (38%), ciprofloxacin (36%), gentamicin (30%), or cefepime (26%), and *S. pneumoniae* nonsusceptible to penicillin (38%), erythromycin (37%), or levofloxacin (1%). Differences in resistance trends were noted based on geographic distribution.
CONCLUSION: MRSA, VRE faecium and multidrug-resistant *P. aeruginosa* are common pathogens in US community hospitals. Ongoing surveillance should be established to detect changes in pathogen frequency or susceptibility changes.

127E. Antifungal activity of amphotericin B (AmB), fluconazole (FLU), and voriconazole (VOR) in an in vitro model of *Candida* catheter-related blood stream infection (CRBSI). *Russell E. Lewis, Pharm.D.,* Dimitrios P. Kontoyiannis, M.D., Sc.D., Rabih H. Dariouche, M.D., Issam I. Raad, M.D., Randall A. Prince, Pharm.D.; University of Houston; University of Texas M.D. Anderson Cancer Center; Baylor University, Houston, TX.

BACKGROUND: Using an in vitro model of infection, we evaluated the activity of 5 simulated antifungal regimens for eradication of *Candida* CRBSI.
METHODS: Single-lumen CVCs were colonized with *Candida species* by sequential incubation in human plasma, then inoculation with ($1x10^5$ CFU/ml) of *C. albicans*, *C. glabrata*, or slime-producing *C. parapsilosis*. Selected catheters were examined by electron microscopy (EM) to confirm the presence of biofilm-encased yeast. Colonized CVCs were then placed in a one-compartment pharmacodynamic model that was used to simulate 5 regimens (plus control): 1) AmB 1.0 mg/kg q24h, 2) AmB 0.5 mg/kg q24h, 3) FLU 400 mg q24h, 4) FLU 800 mg q24h, and 5) VOR 200 mg q12h. At serial timepoints after antifungal therapy was begun, samples were removed from the model via the catheter and a peripheral port for quantitation of viable organisms (CFU/ml). Additionally, individual CVCs were serially removed to quantitate CVC-adherent organisms by the sonication method. Drug concentrations in the model were analyzed by HPLC.
RESULTS: All antifungal regimens significantly suppressed fungal counts by peripheral and catheter sampling (p=0.001). No regimen, however, completely eliminated seeding or eradicated (by culture and EM) CVC colonization. Regrowth was noted in the model for triazole therapy against *C. glabrata*. However, MICs for these organisms were not elevated. Antifungal activity ranked: AmB 1 > AmB 0.5 ≥ VOR > FLU 800 ≥ FLU 400.
CONCLUSION: Neither Amphotericin B or azole therapy completely eradicated *Candida* CRBSI in vitro. Lack of activity against biofilm-encased organisms appeared to be the reason for mycological failure.
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128E. Pretreatment with itraconazole (ITRA) attenuates the efficacy of increasing amphotericin B (AmB) dosages in a murine model of invasive pulmonary aspergillosis (IPA). *Russell E. Lewis, Pharm.D.,* Randall A. Prince, Pharm.D., Dimitrios P. Kontoyiannis, M.D., Sc.D.; University of Houston; University of Texas M.D. Anderson Cancer Center, Houston, TX.

BACKGROUND: Antagonism has been described in vitro and in vivo for azole-polyene combinations against *Aspergillus* species. Little is known, however, about the in vivo pharmacodynamics of azole-polyene interactions. Using an established murine model of IPA (Infect Immun 1989;57:1452-6), we evaluated the efficacy of several AmB dosages given alone, or following treatment with ITRA.
METHODS: Female Swiss-Webster mice (20-25 g) were immunosuppressed with cortisone acetate (250 mg/kg) and cyclophosphamide (150 mg/kg) on day-4 and day-1. Under anesthesia, mice (n=5 per dose) were intranasally inoculated (30 µl) with a standardized conidial suspension ($2x10^8$ CFU/ml) of *A. fumigatus* 293. After 24 hours, AmB was administered by intraperitoneal injections (0.25, 0.5, 1.0, and 3.0 mg/kg) administered daily up to 96 hours after infection. ITRA pre-treatment was given by oral gavage (50 mg/kg twice daily) from day-3 to day-1. Serum drug concentrations were verified by HPLC. Three different end-points for efficacy were used: mortality at 96 hours, viable counts from harvested lung tissue (CFU/ml), and the total lung chitin assay.
RESULTS: At AmB dosages > 1 mg/kg/day, fewer ITRA pretreated mice versus untreated mice were alive at 96 hours (0-20% vs 60-80%, respectively). At all timepoints, fungal lung burden was consistently and significantly higher in the ITRA pre-treated group versus untreated as measured by the CFU counts (p= 0.001) and the chitin assay (p= 0.03).
CONCLUSIONS: ITRA pre-treatment is associated with poorer mycological efficacy and survival in mice treated subsequently with AmB for IPA. Higher doses of amphotericin B do not reverse this antagonism.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, Chicago, IL, September 22-25, 2001.

129. Species distribution and antifungal susceptibility of *Candida* species at an oncology-specialty hospital. Russell E. Lewis, Pharm.D., Melinda Neuhauser, Pharm.D., Jeffrey Tarrand, M.D., Dimitrios P. Kontoyiannis, M.D., Sc.D.; University of Houston; University of Texas M.D. Anderson Cancer Center, Houston, TX.

BACKGROUND: In 1999, our institution implemented routine susceptibility testing for yeast isolated from "sterile" clinical specimens. The purpose of this study was to assess susceptibility patterns for common antifungals used at an oncology-specialty hospital.
METHODS: Susceptibility testing was performed on yeast isolates recovered from sterile sites (urine, blood, tissue, or respiratory tract) during 1999-2000. MICs of amphotericin B (AmB), fluconazole (FLU), and itraconazole (ITR) were performed by broth microdilution (NCCLS M27-A). Susceptibility breakpoints [susceptibility (S) vs susceptible dose dependent (SDD)] were evaluated per NCCLS guidelines and proposed breakpoint criteria.
RESULTS: 460 isolates were obtained from 1999-2000 (n=212, 1999; n=248, 2000). *C. albicans* (49%) was the most common species, followed by the non-*albicans* species *C. glabrata* (27%), *C. tropicalis* (13%), *C. krusei* (10%), and *C. guilliermondii* (1%). Susceptibility rates for 1999-2000 were:

	C. albicans (n= 225)	*C. glabrata* (n=126)	*C. tropicalis* (n=59)	*C. krusei* (n=45)	*C. guilliermondii* (n=5)
%	S/SDD	S/SDD	S/SDD	S/SDD	S/SDD
AmB	98/-	96/-	94/-	75/-	100/-
FLU	93/4	45/42	71/5	0/2	60/40
ITR	73/18	6/30	51/34	8/76	20/20

CONCLUSIONS: AmB was the most consistently active agent of all antifungals tested. Because of the relatively high percentage of isolates exhibiting SDD susceptibility to triazoles, higher than normal dosing may be necessary if these agents are used for empiric therapy (i.e., FLU ≥ 800 mg/day). ITR did not appear to have improved susceptibility over FLU for the non-*albicans* species.

130. In vitro activity of posaconazole, voriconazole, fluconazole, itraconazole, and amphotericin B against bloodstream infections due to *Candida* spp. *David S. Burgess, Pharm.D.*; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX.

PURPOSE: Candida is the fourth leading cause of nosocomial bloodstream infection, consequently the development of new antifungal agents has become very important. This study compared the in vitro activity of 2 investigational triazoles, posaconazole and voriconazole, to fluconazole, itraconazole, and amphotericin B for *Candida* spp. that caused bloodstream infections.
METHODS: All bloodstream isolates due to *Candida* spp. between January 1995 and December 2000 were obtained from the clinical microbiology laboratory. MICs were determined by the NCCLS microdilution for posaconazole, voriconazole, fluconazole, itraconazole, and amphotericin B. For the triazoles, the MIC was defined as the lowest concentration which resulted in 80% reduction in turbidity as compared to a drug-free control tube. For amphotericin B, the MIC was the lowest concentration that inhibited growth to the unaided eye.
RESULTS: A total of 150 *Candida* bloodstream isolates were evaluated, including 55 *C. albicans*, 44 *C. glabrata*, 28 *C. tropicalis*, and 23 *C. parapsilosis*. No duplicate isolates were included in this study.

Organism	Ampho B MIC_{50}/MIC_{90}	Fluconazole MIC_{50}/MIC_{90}	Itraconazole MIC_{50}/MIC_{90}	Voriconazole MIC_{50}/MIC_{90}	Posaconazole MIC_{50}/MIC_{90}
C. albicans	0.5/1	0.25/1	0.03/0.25	0.03/0.25	0.03/0.25
C. glabrata	1/4	4/16	1/2	0.13/0.25	1/2
C. tropicalis	1/2	0.25/2	0.03/0.13	0.06/1	0.06/0.13
C. parapsilosis	0.25/1	0.5/4	0.03/0.13	0.02/0.06	0.03/0.13

CONCLUSIONS: *C. glabrata* had the highest MICs for each antifungal agent except voriconazole. Generally, the newer antifungal agents, posaconazole

and voriconazole, have excellent in vitro activity against these Candida isolates causing bloodstream infections. The clinical relevance of these in vitro results needs to be determined in clinical trials.

131. Effect of demographic, social, and clinical variables, on mortality and length of hospitalization of community-acquired pneumonia. David S. Burgess, Pharm.D., Thomas C. Shank, Pharm.D., *Donna R. Burgess, R.Ph.,* Jane Mondino, Pharm.D., Nishat Patel, Pharm.D., Renee Bellanger, Pharm.D.; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; Baptist Health System, San Antonio, TX.

PURPOSE: Community-acquired pneumonia (CAP) results in significant morbidity, mortality, and cost. We evaluated the effect of numerous variables on mortality and length of stay.
METHODS: We evaluated demographic, social, and clinical data, admission location, length of stay (LOS), mortality, time to clinical stability, and antibiotic therapy on all adult patients admitted for CAP between 1 November 1999 and 30 April 2000. Pneumonia Severity of Illness (PSI) score was calculated to determined severity of disease. Time to clinical stability was defined as temp ≤ 99°F, O_2 saturation ≥ 92%, respiratory rate ≤ 24 breaths/min, heart rate ≤ 100 beats/min, able to eat, and baseline mental status. Cox proportional hazard model and robust regression analysis were utilized to evaluate the relationship between variables and outcomes.
RESULTS: A total of 843 CAP patients were admitted to the hospital 649 general medical ward, 133 ICU, and 61 intermediate care ward. The mean ± SD age was 72 ± 16 with 57% being females. The majority of the patients were Caucasian (54.2%) followed by Latin American (37.6%), African/American (6.8%), and Other (1.4%). Time to clinical stability, LOS, and mortality were 2.4 days, 5.1 days, and 7.4%, respectively. PSI score and ICU care were significantly ($p<0.001$) associated with both mortality and LOS. Time to clinical stability was associated ($p=0.04$) with mortality, and Latin American race was associated ($p=0.006$) with LOS.
CONCLUSION: Atypical antibiotic coverage and time to first antibiotic dose did not significantly effect mortality or LOS. PSI score ICU care, and time to clinical stability were related to mortality while PSI score, ICU care, and Latin American race were related to LOS.

132. Comparison of Etest with NCCLS method for antifungal susceptibility testing of *Candida* spp. to posaconazole. *David S. Burgess, Pharm.D.*; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX.

PURPOSE: Since Candida is the fourth leading cause of nosocomial bloodstream infection, the development of new antifungal agents has become very important. Furthermore, the microbiology laboratory has gained greater attention in the selection, testing, and monitoring of antifungals. The NCCLS Subcommittee on Antifungal Susceptibility Testing developed a standard testing guideline for susceptibility testing of *Candida* spp. However, the method is time-consuming and cumbersome. This study compared the NCCLS microdilution and Etest (AB-Biodisk, Sweden) MICs of posaconazole, an investigational triazole, for *Candida* spp.
METHODS: All bloodstream isolates due to *Candida* spp. between January 1995 and December 2000 were obtained from the clinical microbiology laboratory. MICs were determined by the NCCLS microdilution (M27A) and Etest according to manufacturer recommendations for posaconazole against each *Candida* spp. The MIC_{50}, MIC_{90}, and percent agreement (± 2-dilutions) were determined.
RESULTS: A total of 150 candida bloodstream isolates were evaluated, including 55 *C. albicans*, 44 *C. glabrata*, 28 *C. tropicalis*, and 23 *C. parapsilosis*. No duplicate isolates were included in this study. Overall, the NCCLS and Etest MIC_{50}/MIC_{90} (µg/ml) were 0.0625/2 and 0.064/0.5, respectively with a 92% agreement between Etest and NCCLS MICs. The MIC_{50}/MIC_{90} (µg/ml) by broth microdilution and Etest MICs as well as the percent agreement between NCCLS and Etest MICs for each *Candida* spp. are as follows:

		Broth Microdilution		E test		
	No. of Isolates	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	% Agreement
C. albicans	55	0.03	0.25	0.02	0.09	91%
C. glabrata	44	1.00	2.00	0.50	2.00	93%
C. tropicalis	28	0.06	0.13	0.13	0.50	100%
C. parapsilosis	23	0.03	0.13	0.02	0.05	83%

For each species except *C. tropicalis*, the Etest MICs were usually lower than the NCCLS results.

CONCLUSIONS: The Etest had very good agreement with the NCCLS microdilution method and represents an easier, simple, convenient, and less labor-intensive method for testing the susceptibilities of *Candida* spp. to posaconazole.

133. Using pharmacokinetic/pharmacodynamic indices to guide empiric therapy against *Pseudomonas aeruginosa* in a 700-bed private, university affiliated teaching hospital. *John Mohr, Pharm.D.,* Audrey Wanger, Ph.D., Tracey Goldsmith, Pharm.D., John Rex, M.D.; Memorial Hermann Hospital; University of Texas Health Science Center at Houston, Houston, TX.

PURPOSE: The purpose of this study is to determine which empirical antibiotic regimens are most likely to achieve an AUC/MIC of > 125 SIT^{-1}* hr against *Pseudomonas aeruginosa* in a 700-bed-private, university affiliated teaching hospital.
METHODS: MICs for cefepime, piperacillin, imipenem/cilastatin, gentamicin, tobramycin, amikacin, levofloxacin, and ciprofloxacin were obtained by E-test® for 50 strains of *P. aeruginosa* isolated from ICU patients at Memorial Hermann Hospital. The $AUC_{0\text{-}24h}$ was obtained from pharmacokinetic clinical trials in critically ill patients where appropriate and available or the package insert. The AUC/MIC is calculated as the 24-hour serum AUC divided by the MIC of the pathogen. The AUC/MIC for combination antibiotic regimens is the sum of the AUC/MIC of the individual antibiotics.
RESULTS: When used as monotherapy, the anti-pseudomonal β-lactam antibiotics gave an AUC/MIC ratio ≥ 125 SIT^{-1}* hr against *P. aeruginosa* with only 10% to 68% of the isolates. The addition of a aminoglycoside, preferably tobramycin, or a fluoroquinolone to cefepime, piperacillin, or imipenem increased the probability of achieving an AUC/MIC > 125 SIT^{-1}* hr to 76%-95%. The addition of tobramycin to cefepime, piperacillin, or imipenem gave an 89-95% probability of an AUC/MIC >125 SIT^{-1}* hr. Adding a fluoroquinolone to an anti-pseudomonal β-lactam yielded an AUC/MIC ratio >125 SIT-1* hr in 79-89% of cases.
CONCLUSION: Combination antibiotic therapy with an anti-pseudomonal β-lactam and tobramycin should be used as empiric therapy when *P. aeruginosa* is a concern. In patients where there is an absolute contraindication to aminoglycosides, addition of a fluoroquinolone is not quite as effective but could be considered as a second-line choice.

134. A retrospective analysis of the efficacy and safety profile of oral ciprofloxacin in the treatment of urinary tract infections. Allen Heyd, Ph.D., Daniel Haverstock, M.S., *Randy Pryka, Pharm.D.*; Bayer Corporation, West Haven, CT.

PURPOSE: To compare safety and efficacy of ciprofloxacin in the treatment of urinary tract infections (UTIs) with comparator antimicrobials, specifically TMP/SMX.
METHODS: Retrospectively reviewed 19 prospective, controlled/uncontrolled UTI clinical trials in the US Bayer ciprofloxacin database that included patients treated for uncomplicated (100 mg or 250 mg BID, 3 days), mild/moderate (250 mg BID, 7-14 days) and severe/complicated UTI (500 mg BID, 7-14 days).
RESULTS: Of 4718 patients in 19 clinical trials, 2709 and 2009 received ciprofloxacin or comparator agents, respectively. Of the 2709 patients enrolled in the ciprofloxacin regimen, 68% and 70% were bacteriologically and clinically valid for efficacy evaluation, respectively. Correspondingly, the 2009 patients treated with comparator antimicrobials were 67% bacteriologically and 70% clinically valid. The bacteriological and clinical outcomes for patients treated with ciprofloxacin were 94% eradication and 97% clinical success, while the comparators' outcomes were 91% vs 93%, respectively. Among ciprofloxacin-treated patients, treatment-emergent adverse events were reported less often compared with the control group (24% vs 34%, respectively) and with TMP/SMX-treated patients (28% vs 36%, respectively). Discontinuation due to any adverse event was reported in 1%, 1% and 4% of ciprofloxacin patients treated for uncomplicated, mild/moderate, and severe/complicated UTI, respectively. The discontinuation rates for patients who received comparator antimicrobials were higher (3%, 5% and 9% for the 3 treatment regimens).
CONCLUSIONS: Ciprofloxacin is safe and effective for the treatment of UTIs. Cipro was better tolerated and had higher success rates than TMP/SMX, independent of therapy duration. Ciprofloxacin should be considered as a drug of choice in treating UTIs empirically.

135E. Moxifloxacin vs amoxicillin/clavulanate in the treatment of acute maxillary sinusitis: efficacy, safety and patient-reported outcomes in primary care. *Steve Rakkar, M.D.*; Plano Medical Center, Plano, TX.

PURPOSE: Efficacy, safety, and patient-reported outcomes variables were compared between moxifloxacin (MXF) and amoxicillin/clavulanate (AC) for the management of AMS in the primary care setting.
METHODS: In this prospective, multicenter, non-blinded phase IIIb trial, patients with symptoms of AMS were randomized to receive a 10-day oral regimen of either MXF (400 mg once-daily) or AC (875 mg twice-daily). Clinical success at the test-of-cure (TOC) visit (post-therapy days 14-21) was the primary efficacy measure. Secondary outcomes included rate of clinical relapse at follow-up (post-therapy days 26-46) and evaluation of patient-reported outcomes. Safety data was also tabulated for intent-to-treat (ITT) patients.
RESULTS: Of 471 adults comprising the ITT population (234 MXF, 237 AC), MXF treatment was statistically equivalent to AC at the TOC visit (85.2% vs 81.8%; 95% CI -6%,13%). Per-protocol analysis also confirmed statistical equivalence between MXF and AC (86.5% vs 83.6%; 95% CI -7%,13%). Rates of relapse were similar for the ITT (4% MXF, 5% AC) and the per-protocol (4% both) populations. The frequency of drug-related adverse events were similar between MXF (30%) and AC (25%) and were primarily

gastrointestinal-related: nausea (11% MXF, 5% AC) and diarrhea (3% MXF, 10% AC). At the TOC visit, significantly more MXF-treated patients (n=47; 24%) in the ITT population than AC -treated patients (n=28; 14%) reported symptomatic improvement by day 3 ($p < 0.02$).
CONCLUSIONS: Once-daily MXF was as effective and safe as twice-daily AC in the treatment of AMS. In some patients, MXF was associated with more rapid symptomatic relief.
Presented at the 7th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, Arlington, VA, May 20-23, 2001.

136E. Efficacy and safety of sequential (IV to PO) moxifloxacin for treatment of community-acquired pneumonia due to atypical pathogens. L. Scott Larsen, M.D., *Shurjeel H. Choudhri, M.D.,* Daniel Haverstock, Patricia Jackson, Deborah Church, M.D.; Fusion Clinical Trials, Red Bank, NJ; Bayer Corporation, West Haven, CT.

PURPOSE: Atypical organisms are increasingly reported as etiologic agents in community-acquired pneumonia (CAP), with multiple antibiotics often used to cover both typical and atypical pathogens. In two prospective, randomized, double-blind studies, IV/PO moxifloxacin (MXF) was compared to IV/PO comparators (CMP) for hospitalized patients with CAP. Pooled data are presented for the subset of patients with atypical pathogens.
METHODS: Study 1 subjects received 7-14d IV/PO MXF 400 mg QD or IV/PO amoxicillin clavulanate 1200/625 mg TID ± clarithromycin 500 mg BID. Study 2 subjects received 7-14d IV/PO MXF 400 mg QD, IV/PO alatrofloxacin/trovafloxacin 200 mg QD, or IV/PO levofloxacin 500 mg QD. Endpoint was clinical success at the test-of-cure (TOC) visit (7-30 days post therapy) for microbiologically valid patients (clinically-valid patients with identified pre-therapy pathogens). Methods of bacterial identification included acute/convalescent serology, culture, PCR, and urine antigen tests for *Legionella*
RESULTS: 39 MXF- and 47 CMP-treated subjects (mean age 52 years) had atypical pathogens and were microbiologically valid. Clinical and bacteriological success rates were 95% for MXF- and 94% for CMP-treated subjects at the TOC visit. For MXF- and CMP-treated patients, respective confirmed or presumed eradication rates for specific pathogens were 96% (22/23) vs 97% (29/30) for *Mycoplasma pneumoniae*; 93% (13/14) vs 92% (12/13) for *Chlamydia pneumoniae*; and 100% (2/2) vs 83% (5/6) for *L. pneumophila*. All study drug regimens were well tolerated.
CONCLUSIONS: Sequential IV/PO MXF 400 mg QD was as safe and effective as other fluoroquinolones and a β-lactam/macrolide combination for treating hospitalized patients with CAP due to atypical pathogens.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

137. Moxifloxacin (IV/PO) for patients with severe community-acquired pneumonia. Colby Grossman, M.D., Shurjeel Choudhri, M.D., *Daniel Haverstock,* Patricia Jackson, Deborah Church, M.D.; Palmetto Internal Medicine, Summerville, SC; Bayer Corporation, West Haven, CT.

PURPOSE: In two prospective, randomized, double-blind studies, IV/PO moxifloxacin (MXF) was compared to IV/PO comparators (CMP) for hospitalized patients with community-acquired pneumonia (CAP). Pooled data are presented for the subset of patients with severe pneumonia.
METHODS: Severe CAP was defined as the presence of at least 1 of the following: respiratory rate >30 bpm, P_aO_2/FIO_2 ratio <250 mm Hg; mechanical ventilation; bilateral/multilobar involvement; increases in opacity on chest x-ray by ≥50% within 48h of admission; or presence of shock. Study 1 subjects received 7-14d IV/PO MXF 400 mg QD or IV/PO amoxicillin clavulanate 1200/625 mg TID ± IV or PO clarithromycin 500 mg BID. Study 2 subjects received 7-14d IV/PO MXF 400 mg QD, IV/PO alatrofloxacin/trovafloxacin 200 mg QD, or IV/PO levofloxacin 500 mg QD. Endpoint was clinical success 5 to 30 days post therapy)
RESULTS: Bilateral or multilobar pneumonia was the primary reason for categorization with severe CAP, accounting for 49% of the severe cases. Clinical success rates were 88% (167/190) for MXF- and 83% (155/186) for CMP-treated subjects. Frequencies of drug-related serious adverse events (SAEs) were 6% for both MXF- (15/241) and CMP-treated (155/186) patients. Rates of premature discontinuation due to AEs were 11% for both MXF- (26/241) and CMP-treated (27/238) groups. Corresponding mortality rates were 6% (15/241) and 10% (24/238) respectively. No increase in cardiac morbidity or mortality due to QTc prolongation was noted in either treatment group.
CONCLUSIONS: Sequential IV/PO MXF 400 mg QD was as safe and effective as other fluoroquinolones and a β-lactam/macrolide combination for treating hospitalized patients with severe CAP.

138E. Efficacy of moxifloxacin for treatment of community-acquired pneumonia due to penicillin resistant *Streptococcus pneumoniae*. Dr. Charles Fogarty, *Shurjeel H. Choudhri, M.D.,* Daniel Haverstock, Patricia Jackson, Deborah Church, M.D.; Lung and Chest Medical Associates, Spartanburg, SC; Bayer Corporation, West Haven, CT.

PURPOSE: Recent IDSA guidelines recommend the newer fluoroquinolones for the empiric treatment of community-acquired pneumonia (CAP) infections due to penicillin resistant *S. pneumoniae* (PRSP). In multiple comparative and non-comparative studies, the efficacy of monotherapy with moxifloxacin (MXF: IV and/or PO) for the treatment of CAP was investigated. Pooled data are presented for the subset of patients with CAP due to *S. pneumoniae*.
METHODS: Patients from contributing studies received once-daily 400 mg MXF. PO therapy was provided for 10 days, IV/PO for 7-14 days. Penicillin resistance (MIC ≥ 2 µg/ml) was determined by E-test and confirmed by broth dilution for 12 of 19 PRSP isolates. The primary endpoint was clinical success at the test-of-cure (TOC) visit (7-30 days post therapy) for clinically valid patients who had a culture positive for *S. pneumoniae*.
RESULTS: 164 MXF- and 129 comparator-treated (CT) patients were microbiologically valid with *S. pneumoniae* identified pretherapy. Overall clinical success rates were 91% (149/164) for MXF- and 86% (111/129) for CT-treated subjects at the TOC visit. Corresponding clinical success rates for CAP due to PRSP were 89% (17/19) and 83% (5/6). PRSP confirmed or presumed eradication rates paralleled clinical success rates for both groups. Corresponding confirmed or presumed eradication rates for PSSP (MIC<2 µg/ml) were 92% (129/140) and 86% (93/108). One patient with PRSP bacteremia was identified in the pooled analyses, this patient was successfully treated with MXF.
CONCLUSIONS: A pooled analysis of MXF CAP trials demonstrates MXF to be an effective treatment for CAP due to PRSP.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

139E. Clinical efficacy and pharmacoeconomics of piperacillin/tazobactam administered by continuous versus intermittent infusion. *Joseph L. Kuti, Pharm.D.,* Edward M. Grant, Pharm.D., David P. Nicolau, Pharm.D., Charles H. Nightingale, Ph.D., Richard Quintiliani, M.D.; Hartford Hospital, Hartford, CT.

PURPOSE: Administration by continuous infusion (CI) maximizes the pharmacodynamic profile of the β-lactams by maximizing time above the MIC. Herein, we describe the clinical and economic outcomes associated with an institutional program administering piperacillin/tazobactam by CI versus intermittent infusion (II).
METHODS: Hospitalized patients for whom piperacillin/tazobactam II (3.375 g q6h or 4.5 g q8h) was initially prescribed were prospectively dosed with 8/1 g or 12/1.5 g CI, based on renal function and classification of community- or nosocomial-acquired infection, respectively. Clinical and microbiological success with economic data obtained from the CI group were compared with a sequential historic control of patients treated with the II regimen.
RESULTS: Forty-seven patients received piperacillin/tazobactam by CI and 51 by II. Demographic variables, including length of therapy, were comparable between CI and II regimens. Clinical and microbiological success was similar between groups (94% clinical success in CI vs 82% in II, p=0.081, 89% microbiologic success in CI vs 73% in II, p=0.092). Although there was no significant difference in days to WBC normalization (2.8 ± 2.4 CI vs 3.9 ± 2.2 II, p=0.065), days to normalization of fever (1.2 ± 0.8 CI vs 2.4 ± 1.5 II, p=0.012) were significantly less for the CI regimen. Drug acquisition, preparation, supply and administration costs were significantly less for the CI regimen ($336.60 ± 246.89 CI vs $464.40 ± 422.03 II, p=0.010).
CONCLUSIONS: Administration of piperacillin/tazobactam by continuous infusion provided equivalent clinical and microbiological outcomes with those of intermittent infusion, while significantly improving the rate of response to therapy and lowering associated costs.
Presented at the American Society of Health-System Pharmacists Midyear Clinical Meeting, Las Vegas, NV, Dec 3-6, 2000.

140. Linezolid anaphylaxis and successful oral desensitization in a patient with myasthenia gravis. *Amy Sbaiti, Pharm.D.,* Ozana Lipka, Pharm.D., Michael Cawley, Pharm.D.; Crozer-Chester Medical Center, Upland, PA.

PURPOSE: To describe a successful desensitization protocol in a patient with myasthenia gravis who developed an anaphylactic reaction to linezolid.
METHODS: A 41-year-old woman with a history of myasthenia gravis was initiated on linezolid for treatment of recurrent *enterococcus faecium* bacteremia. Following the first dose of linezolid, the patient developed an anaphylactic reaction. The patient had previously been exposed to linezolid without complications. Desensitization procedure to linezolid was initiated. Because the oral formulation was not available, the intravenous (IV) formulation was selected for greater dose accuracy. A 600 mg IV dose was sequentially divided into fifteen serial dilutions and administered orally at 20-minute intervals. The first twelve doses were administered orally; the last three were administered by dividing the oral tablet.
RESULTS: During the third dose the patient developed mild pruritis and erythema of the arms and upper torso. The third dose was repeated twenty minutes later followed by diphenhydramine, resulting in resolution of symptoms. The remaining doses were administered without event. Following desensitization, therapy was continued with 600 mg orally every twelve

hours.
CONCLUSIONS: Desensitization of a patient with a history of myasthenia gravis and an anaphylactic reaction to linezolid was successfully achieved by sequential oral administration of both the intravenous and tablet formulations of the drug.

141E. Liposomal amphotericin B attenuates concentration-dependent upregulation of neutrophil adhesion. *Christopher J. Andrews, Pharm.D.,* Daniel P. Healy, Pharm.D., FCCP, Alice N. Neely, Ph.D., Ian A. Holder, Ph.D., George F. Babcock, Ph.D.; University of Cincinnati; Shriners Hospitals for Children, Cincinnati, OH.

BACKGROUND: We have previously shown that amphotericin B (amB) increases expression of an important adhesion molecule (CD11b) on neutrophils (PMNs) in a concentration-dependent manner.
AIM: To compare the concentration-effect relationships of deoxycholate (DamB) vs new liposomal (LamB) formulations on PMN CD11b.
METHODS: Heparinized whole blood was incubated with/without *C. albicans* (2.5×10^3 CFU/ml) plus clinical levels of DamB (0.625-10 µg/ml) or Lamb (12.5–200 µg/ml). Cells were stained with PE-labeled anti-CD11b and read by flow cytometry. Receptor expression was assessed by mean fluorescence. Supernatants were assayed for TNF and IL-8 by ELISA. Experiments were performed in triplicate.
RESULTS: The maximum effects (Emax) of DamB vs LamB on CD11b were increases of 237 ± 98% vs 140 ± 81% ($p<0.05$), respectively vs control cells. There was a strong association between DamB concentration and CD11b ($r=0.97$, $p=0.005$; range: 78% increase at 0.625 µg/ml to 265% at 10 µg/ml). These changes were correlated with the rate of fungal cell killing, TNF and IL-8 concentration ($r> 0.9$, $p< 0.01$). In contrast, the association between LamB concentration and increased CD11b was not significant ($r=0.61$, $p=0.26$). TNF and IL-8 levels were lower with LamB while the rate of fungal cell killing was similar.
CONCLUSION: DamB increased PMN CD11b expression in a concentration-dependent manner that was strongly associated with fungal cell killing, TNF and IL-8 release. The LamB formulation attenuated the CD11b response and TNF/IL-8 release despite similar killing curves. The clinical meaning of these differences between formulations is not known.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, Sept 22-25, 2001.

142. Ciprofloxacin vs trimethoprim/sulfamethoxazole for treatment of outpatient adults with lower urinary tract infections: a primary care experience trial. *N.R. Zinner, M.D., M.S.,* K. Hendrick, M.D.; Western Clinical Research, Torrance, CA; Flushing Family Care, Flushing, MI.

PURPOSE: To evaluate efficacy and safety of ciprofloxacin (CIP) and trimethoprim/sulfamethoxazole (TMP/SMX) for adults with symptomatic lower urinary tract infections (UTIs) using an empiric "real-world" approach.
METHODS: A prospective, open-label, outpatient multicenter trial was conducted in a primary care setting. Patients were randomized 2:1 to CIP 250 or 500 mg PO, BID for 3-14 days or TMP/SMX 160/800 mg PO, BID for 10-14 days. The primary efficacy parameter was clinical response at Test-of-Cure (TOC), 4-18-days post-therapy, for the intent-to-treat population (ITT).
RESULTS: From 109 centers, 704 (485 CIP, 219 TMP/SMX) patients comprised the ITT population. Both treatment groups were well balanced, except that severe UTI was higher in the CIP (19%) vs TMP/SMX group (8%). CIP was associated with a significantly higher clinical cure rate (90%) compared with TMP/SMX (82%; 95% CI 1.2, 15.3). Of the 235 pretherapy *Escherichia coli* isolates obtained, 98% were susceptible to CIP, whereas resistance to TMP/SMX was 19%, ranging from 5% (East North Central US states) to 32% (Mid-Atlantic states). Accordingly, TMP/SMX-treated patients required post-therapy urine C&S tests significantly more often than CIP-treated patients ($P \leq 0.03$). Additionally, drug-related adverse reactions were reported more frequently for TMP/SMX- (13.7%) vs CIP-treated patients (8.7%); adverse events were responsible for a 3-fold higher premature discontinuation rate in the TMP/SMX (9%) compared with the CIP group (3%).
CONCLUSIONS: CIP was at least clinically equivalent to TMP/SMX for empiric treatment of symptomatic UTIs. TMP/SMX had higher rates of resistance against *E. coli* and required premature discontinuation due to adverse events and repeat urine C&S more often than CIP.

143. A study of the resistance and its mechanism of clinical staphylococcus aureus against fluoroquinolones. Yusheng Wang, *Xiaohong Song*; West China University of Medical Sciences, Chengdu, China.

PURPOSE: To investigate the antibacterial activity of fluoroquinolones and the mechanism of resistance to fluoroquinolones in Staphylococcus aureus isolated from patients in Chengdu China.
METHODS: The in-vitro activities of fluoroquinolones (norfloxacin, ofloxacin, fleroxacin, ciprofloxacin, sparfloxacin and tosufloxacin) against 155 strains clinical isolates of Staphylococcus aureus in Chengdu area were determined with the agar dilution method. The relationship of the point mutations in the gyrA genes and the resistance of the resistance of 63 strains (57 fluoroquinone-resistant strains and 6 wild types) isolated clinically in Chengdu had been investigated by a combination of restriction fragment length polymorphism analysis.
RESULTS: The drug-resistant ratio of norfloxacin, fleroxacin, ciprofloxacin, tosufloxacin, ofloxacin and sparfloxacin was 35.5%, 34.19%, 27.75%, 27.75%, 25.81% and 25.81%, respectively. All of their MIC_{90} were ≥ 16 mg/L. We found that there were 67.27 to ~92.5% of the fluoroquinolone-resistant strains against norfloxacin, fleroxacin, tosufloxacin, ciprofloxacin, ofloxacin and sparfloxacin had a Hinf I site mutation in the gyrA genes, and most of such strains with mutation in the gyrA genes showed high-lever resistance.
CONCLUSION: The results indicated that it was Hinf site mutation of the gyrA genes that mainly cause the resistance of the clinical fluoroquinolone-resistant strains of *Staphylococcus aureus* and we should use antibiotic rationally to decrease the resistant strains.

144. Antibiotic use associated with *Clostridium difficile* colitis before and after a formulary change. *Sheri M. Tokumaru, Pharm.D.,* Robert P. Rapp, Pharm.D., Martin E. Evans, M.D.; University of Kentucky Chandler Medical Center, Lexington, KY.

PURPOSE: This study aimed to determine if 1) the formulary deletion of cefotaxime and ceftazidime from formulary and the addition of cefepime in November 1999 decreased the incidence of *C. difficile* (CD) toxin- positive patients, 2) to determine if there was an association between CD andwith recent use of other antibiotics, and 3) to determine the utilization of different various CD treatment regimens prescribed in the medical center. Ampicillin/sulbactam and piperacillin/tazobactam use was encouraged in addition to the formulary change.
METHODS: Through retrospective chart review, microbiology records, and the clinical database management system, toxin-positive hospitalized adult patients during before (1/1/99through -6/30/99) and after formulary change (1/1/00through -6/30/00), before and after formulary change, were evaluated to determine antibiotic use during admission. Patient demographics and antibiotic use during hospital admission were assessed.
RESULTS: There wereA total of 58 toxin- positive patients and 7812 non-positive patients who received antibiotics during the 1999 study period, while . There were 47 toxin- positive patients and 8251 non-positive patients who received antibiotics during the 2000 studysecond period (p=0.177). There were no significant differences in patient characteristics between the two time periods. During the 1999 time period, ceftazidime (OR 4.1; CI 1.7, 10.3), cefotaxime (OR 6.2; CI 2.3, 16.7), piperacillin/tazobactam (OR 4.6; CI 2.3, 9.3) and ampicillin/sulbactam (OR 2.6; CI 1.2, 5.2) were significantly associated with CD. Following the formulary change, cefepime (OR 6.8; CI 2.8, 16.7), piperacillin/tazobactam (OR 1.7; CI 1.5, 6.8), ampicillin/sulbactam (OR 3.0; CI 1.4, 6.4) and ciprofloxacin (OR 3.0; CI 1.4, 6.3) were significantly associated with CD. There was no difference between the treatment of CD toxin-positive patients between years.
CONCLUSIONS: The formulary addition of cefepime and deletion of cefotaxime and ceftazidime did not change influence the incidenceoverall rate of CD toxin- positive patientspatients. The rate of *C. difficile* did not decrease as expected with this formulary change.

145. Activity of gemifloxacin against levofloxacin-resistant *Streptococcus pneumoniae* by time-kill methodology. *Michael B. Kays, Pharm.D.*; Purdue University, Indianapolis, IN.

PURPOSE: Fluoroquinolone-resistant *Streptococcus pneumoniae* is an emerging concern. Pneumococcal susceptibility testing in Indianapolis found that 1.7% of isolates were resistant to levofloxacin. However, these strains were susceptible to gemifloxacin (MIC ≤ 0.5 µg/ml), an investigational fluoroquinolone. The purpose of this study was to evaluate the bactericidal activity of gemifloxacin against levofloxacin-resistant *S. pneumoniae* (LRSP) by time-kill testing.
METHODS: MICs and time-kill studies were performed against two clinical isolates of LRSP (M3, M205). Levofloxacin and gemifloxacin MICs were performed in triplicate in Todd-Hewitt broth with 0.5% yeast extract (THY). Time-kill studies were performed in 100 ml THY in a shaking water bath at 35°C. The starting inoculum was ≈ 10^6 CFU/ml, and gemifloxacin concentrations of 0.5, 1, 2, 4, and 8 x MIC were tested. Viable colony counts were determined in duplicate at 0, 2, 4, 6, 8, and 12 h (preliminary growth studies showed significant autolysis at 24 h). Recovery plates were incubated up to 48 h at 35°C in ambient air. Bactericidal activity was defined as a ≥ 3-$\log_{10}$ reduction in CFU/ml. DNA sequencing was also performed to characterize the genes in the quinolone resistance-determining region (QRDR).
RESULTS: The M3 and M205 isolates were cultured from sinus and sputum sources, respectively.

	M3 Isolate	M205 Isolate
Gemifloxacin MIC	0.03 µg/ml	0.5 µg/ml
Levofloxacin MIC	8 µg/ml	32 µg/ml
Mutations in QRDR		
gyrA	Ser81→Tyr	Ser81→Phe
parC	None	Ser79→Phe
Δ $\log_{10}$ CFU/ml at 12 h		

0.5x MIC	+ 0.46	+ 0.33
1x MIC	+ 1.10	- 2.18
2x MIC	+ 0.18	- 2.58
4x MIC	- 2.12	- 2.55
8x MIC	- 3.29	- 2.69

For M3, the activity of gemifloxacin was concentration-dependent with greater rate and extent of killing as concentration/MIC ratios increased. For M205, the rate and extent of killing were similar at concentration/MIC ratios ≥ 1. Gemifloxacin was bactericidal at 8x MIC after 12 h for the M3 isolate only.
CONCLUSIONS: Although LRSP may remain susceptible to gemifloxacin, this agent may not provide consistent bactericidal activity against these isolates. Additional in vitro and clinical data are needed to determine the role of gemifloxacin in the treatment of infections caused by LRSP.

Nephrology

146. The influence of renal function on enoxaparin clearance. *Maria C. Pruchnicki, Pharm.D.,* Sandra L. Kane, Pharm.D., M.Sc., Mark E. Boye, M.S., MPH, Mary Beth Bobek, Pharm.D., Joseph F. Dasta, M.Sc.; Ohio State University, Columbus, OH; Cleveland Clinic Foundation, Cleveland, OH.

PURPOSE: The influence of renal function on enoxaparin clearance remains controversial. We studied the association between renal function [creatinine clearance (CrCl)] and enoxaparin elimination (anti-Xa clearance) in hospitalized patients with a wide range of renal function.
METHODS: Medical records of 80 patients receiving continuous enoxaparin infusions during a 24-month period were reviewed. CrCl was estimated by the methods of Cockcroft-Gault or Brater, as appropriate. Only steady-state anti-Xa concentrations (stable dose ≥ 24 hours) for patients with stable renal function (≤ 20% change in CrCl during treatment) were included in analysis; anti-Xa clearance was calculated from the ratio of enoxaparin dose to anti-Xa concentration. The association between these variables was tested by clustered regression analysis with Monte-Carlo simulation.
RESULTS: Thirty-four patients received a mean (± SD) enoxaparin dose of 5.0 ± 1.4 mg/hr and contributed 77 observations. Patients averaged 58 ± 17 years and 70.4 ± 17.9 kg. The mean CrCl and anti-Xa clearances were 53 ± 33 ml/min (8-153 ml/min) and 0.95 ± 0.50 L/hr (0.13-2.50 L/hr), respectively. Regression results suggest little correlation between anti-Xa and creatinine clearances (r^2=0.04; p=0.21). Monte-Carlo results reveal no significant differences between anti-Xa clearances estimated at quartiles of CrCl and an estimated mean anti-Xa clearance of 0.95 L/hr (95% CI 0.78, 1.11 L/hr).
CONCLUSION: Calculated anti-Xa clearances agree with previous reports and did not significantly change over the wide range of observed CrCl. We therefore conclude enoxaparin clearance is unlikely to be associated with renal function.

147. Medication cost and drug related problems in hemodialysis outpatients. *Harold J. Manley, Pharm.D.,* Marcy McClaran, R.N., Bernice Franklin, R.N.; University of Missouri at Kansas City; Dialysis Clinic, Inc, Kansas City, MO.

PURPOSE: Hemodialysis patients are commonly prescribed 8-10 medications, many of them costly. Medicare reimburses (MR) those given during dialysis (e.g., erythropoietin; iron) and reports the costs annually. Costs associated with remaining Medicare non-reimbursed (Non-MR) 5-7 medications are not known. Additionally, hemodialysis patients are at risk for drug-related problems (DRPs) due to complex medication regimens and multiple comorbidities. We conducted a medication review at our dialysis center to identify medication costs and potential DRPs.
METHODS: Patient records were reviewed to identify medical problems, prescribed medications, medication indication(s) and potential DRPs. Medications were classified and average wholesale price determined. DRPs were classified and comparisons were made between diabetic (DM) and non-DM patients. Results were expressed as mean ± SD or percentages.
RESULTS: Patients were 61.0 ± 15 years old, were prescribed 11.0 ± 4.2 medications, and had 6.0 ± 2.3 medical problems. Medication cost/prescription/month was $352.19 ± 469.05 and $42.13 ± 63.82 for MR and Non-MR medications, respectively. Per prescription, Non-MR medication costs were similar to national averages. Patients were prescribed 2.3 ± 0.7 MR and 8.8 ± 4.0 Non-MR medications. Monthly medication cost per patient was $1,125.94 ± 714.51 (median $941.28). A total of 474 potential DRPs were identified, averaging 3.6 ± 1.8 per patient. Drug without indication and indication without treatment accounted for 48% DRPs. Diabetic patients had more DRPs identified than nondiabetics (303 v. 172 DRPs, respectively; p<0.05).
CONCLUSION: Dialysis patients have complex medication regimens that are costly and frequently contain DRPs. Much opportunity for pharmaceutical care exists in this population.

148. Efficacy of alteplase versus urokinase in hemodialysis catheter thrombosis. *Heather M. Eyrich, Pharm.D.,* Ted Walton, Pharm.D., BCPS, Edwin Macon, M.D.; Grady Health System; Emory University, Atlanta, GA.

PURPOSE: The objective of this study was to compare the efficacy of localized administration of alteplase 1 mg/catheter port to urokinase 5000 u/catheter port in restoring adequate hemodialysis (HD) catheter blood flow rates, >300 ml/min, after catheter thrombosis.
METHODS: Medical records and HD flow sheets of 27 patients receiving 43 alteplase doses and 10 patients receiving 20 urokinase doses between June 1997 and December 2000 were reviewed. Pre and post treatment HD blood flow rates, catheter function at subsequent HD session, and need for surgical intervention were evaluated.
RESULTS: HD blood flow rates significantly increased after administration of either thrombolytic agent (alteplase: 116 to 293 ml/min, p<0.01; urokinase: 63 to 203 ml/min, p<0.01). Significantly more patients achieved post treatment blood flow rates > 300 ml/min after treatment with alteplase than urokinase (70% vs 35%, p<0.01). More patients completed HD after treatment with alteplase than with urokinase (93% vs 70%, p<0.05). No relationship between thrombolytic agent and future catheter function was determined. Surgical interventions were required in 23% and 25% of alteplase and urokinase patients respectively.
CONCLUSION: A significant increase in HD blood flow rates was seen after the use of both thrombolytic agents, suggesting alteplase 1 mg/catheter port is as efficacious as urokinase 5000 u/catheter port in restoring HD catheter function after thrombosis. Alteplase treated patients were more likely to achieve goal blood flow rates, >300 ml/min, and to complete HD than urokinase treated patients. Larger prospective trials are needed to confirm these results.

149E. Impact of renal dysfunction on fluconazole dosage requirements. *James D. Coyle, Pharm.D.,* Maria C. Pruchnicki, Pharm.D., William H. Bay, M.D.; Ohio State University, Columbus, OH.

PURPOSE: To determine an appropriate approach to dosing fluconazole in patients with renal dysfunction.
METHODS: A MEDLINE search was performed to identify fluconazole pharmacokinetic and dynamic studies in adult, nondialysis subjects. Based on these manuscripts, a model of fluconazole pharmacokinetics, including an equation relating fluconazole clearance (FlCl) to creatinine clearance (CrCl), was developed. The ability of this model to accurately predict FlCl over a wide range of renal function was assessed by determining the correlation between predicted and reported FlCls, the systematic error (bias) in FlCl predictions, and the typical magnitude of FlCl prediction errors.
RESULTS: Based on thirteen suitable publications, a linear, two-compartment model with input into and elimination from the central compartment, no absorption lag time, Cl=20.85 ml/min (in persons with normal CrCl), V_c=37.31 L, V_{ss}=52.12 L, k_{12}=0.143 hr^{-1}, k_{21}=0.360 hr^{-1}, k_a=1.28 hr^{-1}, and F=0.94 was selected. FlCl (mL/min) was related to CrCl by the equation FlCl = 0.158 x CrCl + 2.30. Reported and model-predicted FlCls were highly correlated (r=0.94, p<0.0001), with a slope and intercept not significantly different from 1 and 0, respectively (p>0.05). The model was an unbiased predictor of FlCl [median prediction error (95% CI)=11.9% (-6.5%, 18.6%]. The typical size of prediction error (95% CI) was 16.1% (6.5%, 23.1%).
CONCLUSIONS: This model accurately predicts FlCl, suggesting that, in contradiction to current recommendations, fluconazole maintenance dose may be decreased in proportion to the decrease in renal function. This approach would maintain equivalent average steady-state fluconazole concentrations while minimizing drug cost and adverse events.
Presented at the World Congress of the American Society of Nephrology and the International Society of Nephrology, San Francisco, CA, October 14, 2001.

150E. Effect of phosphate binders on supplemental iron absorption in healthy subjects. *Maria C. Pruchnicki, Pharm.D.,* James D. Coyle, Pharm.D., William H. Bay, M.D.; Ohio State University, Columbus, OH.

PURPOSE: The hypothesis for this study was that the traditional phosphate binders, calcium carbonate and calcium acetate, decrease gastrointestinal iron absorption while a newer phosphate binder, sevelamer HCl, does not. The purpose of this study was to test this hypothesis by comparing the acute effect of equivalent doses of the three phosphate binders on supplemental iron absorption.
METHODS: The study was a single-dose, prospective, randomized, four treatment, crossover trial with washout. Twenty-three healthy subjects received 65 mg elemental iron (Feosol) alone or with a phosphate binder [calcium carbonate (Tums) 3000 mg; calcium acetate (PhosLo) 2668 mg; or sevelamer HCl (Renagel) 2821 mg]. Plasma iron concentrations were measured over four hours. Area under the change in plasma iron concentration - time curve (AUC) was calculated using the trapezoidal method. Treatment effects were assessed using ANOVA. Statistical significance was defined as p<0.017 to adjust for three comparisons (iron only vs iron plus each phosphate binder).
RESULTS: Subject (52.2% male) mean age was 26 years (range 18-36). The AUC (µg•hr/dl) results were:

	Iron Only	Iron + Tums	Iron + PhosLo	Iron + Renagel
Mean AUC	408.6	322.7	266.1	376.3
SEM	34.2	34.2	23.1	38.2
% change	-	-21.0	-34.9	-7.9
p value	-	0.001	<0.0001	NS

CONCLUSION: Calcium carbonate and calcium acetate significantly reduce absorption of single oral doses of ferrous sulfate, while sevelamer HCl does not. Traditional phosphate binders may therefore complicate anemia management in chronic renal insufficiency patients, although this needs to be confirmed in the appropriate patient population.
Published in Am J Kidney Dis 2001;37:A27.

151. Determination of linezolid clearance via continuous hemodiafiltration. *Laurie S. Mauro, Pharm.D.,* Imran Sharief, M.D., Ragheb Assaly, M.D., Deepak Malhotra, M.D., Ph.D.; University of Toledo; Medical College of Ohio, Toledo, OH.

PURPOSE: Linezolid is being increasingly utilized for life-threatening vancomycin resistant infections in critically ill patients. Limited data suggest that linezolid is cleared by intermittent hemodialysis. However, information on clearance of linezolid by continuous renal replacement therapy is not available. A patient receiving linezolid who was undergoing continuous venovenous hemodiafiltration (CVVHDF) was evaluated to determine linezolid clearance via CVVHDF.
METHODS: A 33-year-old man with necrotizing fasciitis and acute renal failure, requiring CVVHDF, was treated with linezolid 600 mg every 12 hours for a vancomycin resistant urinary tract infection. After 3 days of linezolid therapy, a series of 11 blood samples, and all urine and diafiltrate were collected over a 12-hour period after initiation of a 1 hour linezolid infusion. Linezolid concentrations were determined via HPLC assay. Linezolid clearance via CVVHDF was determined by 2 methods. Method 1 utilized the amount of drug recovered in diafiltrate. Method 2 evaluated plasma drug concentrations in pre- and post-filter (PAN-10 Hemofilter, Asahi Medical Co.) samples. Total body clearance was also determined from area under the curve.
RESULTS: Clearance of linezolid via CVVHDF was found to be 15.6 ml/min by Method 1 and 21.6 ml/min by Method 2. Total body clearance was found to be 189 ml/min. The amount of linezolid recovered in the diafiltrate was 50 mg or 8.3% of the dose.
CONCLUSION: Clearance of linezolid via CVVHDF in this patient was marginal. It does not appear that supplemental dosing of linezolid is necessary in patients undergoing CVVHDF.

152E. The pharmacokinetics of novel erythropoiesis stimulating protein (NESP) following chronic intravenous administration are time-and dose-linear. Michael Allon, M.D., Kenneth Kleinman, M.D., Michael Walczyk, M.D., Charles Kaupke, M.D., Bradley J. Maroni, M.D., *Anne Heatherington, Ph.D.,* Kurt Olson, Ph.D., Louise Messer-Mann, BSN; University of Alabama, Birmingham, AL; South Valley Regional Dialysis Center, Encino, CA; Northwest Renal Clinic Inc., Portland, OR; University of California at Irvine Medical Center, Irvine, CA; Amgen Inc., Thousand Oaks, CA.

PURPOSE: To determine the pharmacokinetics (PK) of NESP (darbepoetin alfa) following chronic intravenous (IV) administration.
METHODS: A multicenter, randomized study was conducted in 47 patients with chronic kidney disease (CKD) receiving hemodialysis. The PK of NESP, administered three times weekly (measured through 48 hours) or once weekly (measured through 168 hours), were compared with IV recombinant human erythropoietin (r-HuEPO), given three times weekly. Patients were administered between 2.6 to 302.0 µg/wk of NESP or 5400 to 42900 U/week of r-HuEPO. The PK profile was measured during weeks 1, 12 and at hemoglobin steady-state (or between weeks 36 and 40, whichever occurred first).
RESULTS: The mean terminal half-life ($t_{1/2,z}$) and clearance values are summarized below.

	NESP 1x/week		NESP 3x/week		r-HuEPO 3x/week	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
$t_{1/2,z}$ (h)						
Week 1	17	17.8 (15.2, 20.4)	11	13.1 (11.2, 14.9)	14	6.3 (5.1, 7.6)
Week 12	14	23.4 (20.6, 26.2)	11	18.3 (14.4, 22.2)	14	8.0 (5.7, 10.3)
Hemoglobin steady-state	11	23.6 (19.2, 28.0)	10	15.7 (12.5, 18.8)	14	8.5 (5.6, 11.5)
Clearance (mL/h/kg)						
Week 1	17	2.00 (1.65, 2.34)	11	2.05 (1.51, 2.59)	14	8.58 (6.72, 10.44)
Week 12	14	1.79 (1.42, 2.17)	11	1.90 (1.31, 2.49)	14	7.51 (6.48, 8.53)
Hemoglobin steady-state	11	1.65 (1.28, 2.03)	10	1.97 (1.50, 2.44)	14	7.67 (6.59, 8.75)

Confirming a previous single-dose PK study, the $t_{1/2,z}$ of the NESP groups were two- to three-fold longer than r-HuEPO. The PK of chronic IV NESP therapy was both dose-and time-linear and there was no evidence of accumulation over 48 weeks of treatment. There was no effect of baseline covariates (demographics, dry weight, baseline hemoglobin, iron indices) on any PK parameter. The safety data were characteristic of CKD patients and there were no trends indicative of a treatment-related effect.
CONCLUSION: The PK of NESP (darbepoetin alfa) does not change as a function of time or dose, despite the less frequent dosing compared with r-HuEPO, and thus may simplify anemia management in CKD patients.
Published in J Am Soc Neph 2000;11:A234.

153. Vancomycin administration with F-8 polysulfone hemodialysis membranes: experience with a post-hemodialysis dosing protocol. *Mary K. Stamatakis, Pharm.D.,* Joy M. Schreiber, R.Ph., Douglas Slain, Pharm.D., BCPS; West Virginia University, Morgantown, WV.

PURPOSE: No information is available in the literature regarding vancomycin removal with F-8 polysulfone hemodialysis (HD) membranes that have medium-flux characteristics. A traditional vancomycin dosage interval of every 7 days is unlikely to maintain concentrations within the therapeutic range. Therefore, frequent vancomycin serum concentration monitoring is required to assist with dosage adjustments. A revised regimen for vancomycin therapy was instituted using a loading dose followed by 7 mg/kg after each dialysis treatment. This report describes the clinical experience using this revised dosing strategy, and compares it with results obtained from traditional dosing.
METHODS: Medical records of HD patients admitted to the hospital from January 2000 through June 2001 were reviewed. Patients were included in the study if they received HD for at least 3 months, received at least 2 dosages of vancomycin, and had at least one vancomycin serum drug concentration (SDC) obtained. Patients were classified as receiving traditional dosing (1-2 g IV every 3-7 days) or post-HD dosing (1-2 g load, followed by 7 mg/kg after each HD session).
RESULTS: Vancomycin was administered to 16 and 24 patients using the traditional and post-HD dosing methods, respectively. There was no difference in demographics, cumulative dose, duration of treatment, drug costs, and number of SDCs between the two groups. However, there was a significantly greater percentage of SDCs within the pre-HD target range of 12-25 µg/ml in the post-HD dosing group (72% vs 45%, $p<0.05$).
CONCLUSIONS: In patients undergoing HD with F-8 dialyzers, vancomycin 1-2 g IV load, followed by 500 mg after HD provides adequate vancomycin SDCs within the target range.

154. Rapid, high-dose intravenous iron sucrose therapy in a Jehovah's Witness patient with chronic renal failure. *Michael H. Schwenk, Pharm.D.,* Daniel A. Blaustein, M.D.; New York Hospital Medical Center of Queens, Flushing, NY; Long Island College Hospital, Brooklyn, NY.

PURPOSE: New parenteral iron products have become available which offer a better safety profile compared to iron dextran. We report data on the safety/efficacy of rapid, high dose intravenous iron sucrose therapy in a severely anemic patient.
METHODS: A female 74-year-old 72.1 kg Jehovah's Witness presented after falling, with dizziness and melena. Endoscopy revealed gastrointestinal bleeding from hemorrhagic gastritis and angiodysplasia of the stomach. She had a history of diabetic nephropathy (CrCL 28 ml/min), multiple GI bleeds, anemia, and iron dextran-induced pruritis and supraventricular and ventricular tachycardia. Hemoglobin/hematocrit/ferritin were 5.8/19.1%/15. She received 500 mg iron sucrose in 0.9% NaCl 150 ml IV over 2-3h QD for 6 days (3000 mg total) and erythropoietin alfa 10,000 units SC and folic acid 1 mg PO daily. After completion of iron sucrose therapy ascorbic acid 500 mg PO daily was added.
RESULTS: There were no acute adverse events associated with the iron sucrose infusions, including blood pressure changes, pruritis, or cardiac arrhythmias. Three days after completion of iron therapy the hemoglobin/hematocrit were 6.4/20%, the transferrin saturation 18.6%, and the ferritin 735. One week after iron sucrose therapy the hemoglobin/hematocrit were 7.6/27.2%, transferrin saturation 12%, and ferritin 925. The corrected reticulocyte count was 4%. The patient felt well, and was discharged 1 week after completion of iron sucrose therapy.
CONCLUSION: This case illustrates the acute safety and efficacy of rapid high dose intravenous iron sucrose therapy in a severely anemic patient. Further data should be gathered to confirm this report.

155E. Novel erythropoiesis stimulating protein (NESPdarbepoetin alfa) safely maintains hemoglobin concentration levels in hemodialysis patients as effectively as r-HuEPO when administered once weekly. *Melanie S. Joy, Pharm.D.,* Gerald A. Hladik, A.R. Nissenson, S.K. Swan, J.S. Lindberg, S.D. Soroka, A.D. McDermott-Vitak, C. Wang, N. Picarello, R. Beatey; University of North Carolina, Chapel Hill, NC; University of California at Los Angeles Medical Center, Los Angeles, CA; Clinical Research Unit of Total Renal Research, Minneapolis, MN; Alton Oschner Medical Foundation, New Orleans, LA; Amgen, Thousand Oaks, CA; Dalhousie University, Halifax, NS, Canada.

PURPOSE: NESP Darbepoetin alfa is a hyperglycosylated erythropoiesis-stimulating protein with a 3-fold longer terminal half-life in man than r-HuEPO. To determine if darbepoetin alfaNESP is safe and effective in maintaining Hgb Hb when administered at a reduced frequency compared with r-HuEPO, a double-blind randomized study comparing IV darbepoetin alfaNESP and r-HuEPO was conducted in North America.
METHODS: Five hundred seven hemodialysis patients were randomized (1:2) to receive either IV darbepoetin alfaNESP once weekly plus placebo 2 times weekly, or to continue to receive IV r-HuEPO 3 times weekly. The dose of study drug was adjusted as necessary to maintain subjects' HgbHb concentrations within -1.0 and +1.5 g/dl of their mean baseline Hgb Hb value and between 9.0 to 13.0 g/dl for up to 28 weeks (20-week dose-titration period followed by an 8-week evaluation period). The primary endpoint was

the change in Hgb Hb level between the baseline and the evaluation period (weeks 21-28).
RESULTS: The mean change (± SD) between baseline and evaluation was 0.16 (± 0.97)g/dl for darbepoetin alfaNESP and 0.0 (± 1.0)g/dl for r-HuEPO. The between-group difference in the mean change in Hgb Hb concentration from baseline to the evaluation period was 0.16 g/dl (95% CI: -0.06, 0.38). This was not a statistically significant or clinically relevant difference despite the reduced frequency of darbepoetin alfaNESP administration, indicating that the efficacy of darbepoetin alfaNESP was similar to r-HuEPO. The percentage of patients with Hgb Hb concentrations defined as unstable (35% darbepoetin alfaNESP, 38% EPO) and the frequency of dose changes were similar between treatment groups during the evaluation period. Adverse events, withdrawals and deaths did not differ in darbepoetin alfaNESP- and r-HuEPO-treated patients.
CONCLUSION: Darbepoetin alfaNESP maintains Hgb Hb as safely and effectively as r-HuEPO while providing the benefit for both patients and health care providers of less frequent dosing.
Published in J Am Soc Nephrology 2000;11:252A.

156E. Long-term effect of paricalcitol in hemodialysis patients. Amy Barton Pai, Pharm.D., Sonia Lin, Pharm.D., Jose A.L. Arruda, M.D., *Alan H. Lau, Pharm.D.*; University of Illinois at Chicago, Chicago, IL.

PURPOSE: There has been limited data regarding the efficacy of long-term use of paricalcitol in hemodialysis patients. This study was conducted to determine the effects of long-term therapy on parathyroid hormone (PTH) suppression and the incidence of elevated serum calcium (Ca), phosphorous (P), and calcium- phosphate product (Ca x P).
METHODS: Patients who received paricalcitol > 3 months had the following data collected: demographics, drug dosage, PTH, corrected calcium, phosphorous and Ca x P.
RESULTS: Sixteen patients (age 45 ± 12 years, 56% male) received paricalcitol for 3-20 months (mean: 12.5 months). The mean dose of paricalcitol used was 0.15 ± 0.12 µg/kg. Mean pre-paricalcitol serum PTH levels were 668 ± 352 pg/ml, which did not change significantly with treatment. The number of patients who had at least one serum Ca ≥ 11.5 mg/dl, one serum P > 6.5 mg/dl, or one Ca x P > 70 were 75%, 88% and 75%, respectively, resulting in 20% of doses being held. The paricalcitol dose at which patients exhibited hypercalcemia ranged from 0.05 µg/kg to 0.23 µg/kg.
CONCLUSION: Paricalcitol was effective in maintaining PTH suppression during this study. Doses that were frequently held secondary to increased Ca and Ca x P may have prevented further PTH reduction. Most patients had elevated Ca, however, the dose threshold was patient-specific.
Published in Clin Pharmacol Ther 2001;69:92.

Neurology

157E. Costs and cost-effectiveness of oxcarbazepine versus sodium valproate for new/recent onset partial seizures. *Steve Karceski, M.D.*; Columbia University, New York, NY.

PURPOSE: To determine the comparative costs and cost-effectiveness of oxcarbazepine (OXC) and sodium valproate (VPA) in the treatment of new and recent onset partial epileptic seizures.
METHODS: Low, moderate and high dose maintenance regimens were determined for each drug based upon prescription audit information. Daily drug costs for each dosage level were computed. A decision-analysis model using a Monte Carlo simulation evaluated the cost-effectiveness of OXC and VPA. The model contained the computed daily drug costs along with direct payer costs associated with initiation and maintenance of therapy, treatment of adverse events and switching from one drug to another due to poor seizure control or adverse events.
RESULTS: The average daily drug costs over the dosage levels were $4.72 ($1.49 to $7.66) for OXC and $3.17 ($2.45 to $3.87) for VPA. Total one-year costs for OXC were $3511 and $5931 for VPA. The computed number of months on initial therapy was 9.95 for OXC and 9.66 for VPA. The analysis was carried out to four years; cost for this time horizon were $20,426 and $23,790 with 25.2 and 24.6 months of therapy for OXC and VPA, respectively.
CONCLUSIONS: These findings suggest that OXC results in lower expected total costs compared to VPA when drug costs, evaluation and management, adverse events and costs of switching therapies are taken into account.
Presented at the meeting of the International Society for Pharmacoeconomics and Outcomes Research, Washington, DC, May 2000.

158E. The prevalence of attention deficit hyperactivity disorder in adults is greater in RLS patients than in controls. *Mary L. Wagner, Pharm.D., M.S.,* Arthur S. Walters, M.D., Barbara C. Fisher, Ph.D., Jasleen Lyall, Abdul Rana, M.D., Cheryl Lebrocq, J.D., Gerry Stefanatos, Ph.D., ABM, Sala Uddin, M.D., Meera Nathan, M.D., Shabana Modan, M.D., Lewis Milrod, M.D., M. Farrukh Nizzam, M.D.; Rutgers University, Piscataway, NJ; JFK Neuroscience Center, Edison, NJ; Brain Evaluation Inc., Washington, MI.

PURPOSE: This study determined the prevalence of attention deficit hyperactivity disorder (ADHD) in adult patients with restless legs syndrome (RLS).
METHODS: Determination of prevalence and severity of ADHD symptoms in 58 adult RLS patients and in 59 adult healthy controls using the Brown ADD scale and DSM-IV criteria for ADHD. RLS prevalence and severity was assessed using International RLS Study group criteria and rating scale. The data were analyzed using ANOVA and Chi-square tests.
RESULTS: The mean ADD score was greater ($p<0.02$) in RLS patients (35 ± 28) than in controls (24 ± 19). Highly probable ADD (score 55) occurred in 20% of RLS patients versus 7% of controls ($p<0.04$) and 16% of the RLS patients met ADHD DSM-IV criteria versus 3% of controls ($p<0.07$). The severity of RLS symptoms was greater ($p<0.001$) in RLS patients with ADD (27 ± 9) than in patients without ADD (20 ± 10). The ADD scores were lower in RLS patients who received dopaminergic drugs (33 ± 27) versus those who did not (42 ± 32; $p>0.05$). A neuropsychologist confirmed results using Neuropsychometric testing.
CONCLUSIONS: RLS patients have a greater prevalence of ADHD and severity of RLS symptoms. RLS leg discomfort and sleep disruption may increase ADHD symptoms. Alternatively, RLS and ADHD may be genetically linked. Dopaminergic medications, used to treat RLS may improve ADHD symptoms and lead to an underestimation of ADD scores and the prevalence and severity of ADHD in RLS patients. Statistical significance may have been achieved if dopaminergic drug doses had been titrated to ADHD symptom relief rather than RLS symptoms.
Published in Neurology 2001;56 (Suppl 3):A4-A5.

159. Evaluation of captopril for the management of hypertension in autonomic dysreflexia: a pilot study. Zahida Esmail, B.Sc.Pharm., *Karen F. Shalansky, Pharm.D., FCSHP,* Rubina Sunderji, Pharm.D., FCSHP, Hugh Anton, M.D., FRCP, Keith Chambers, M.D., M.H.Sc., William Fish, M.D.; Vancouver General Hospital; G.F. Strong Rehabilitation Hospital, Vancouver, BC, Canada.

PURPOSE: Autonomic dysreflexia (AD) is a condition of massive sympathetic discharge which affects patients with spinal cord injuries above the level of T6. Immediate release nifedipine is the current recommended antihypertensive agent to treat hypertensive urgencies in AD. The purpose of this trial is to evaluate the efficacy of captopril in the management of AD.
METHODS: This was a one-year, prospective, open-label pilot study. Twenty-six consecutive patients older than 15 years with spinal cord injury above T6 admitted to a rehabilitation hospital were included. During an AD episode, captopril 25 mg was administered sublingually if systolic blood pressure (SBP) was at or above 150 mm Hg despite the use of non-drug measures. If SBP remained elevated 30 minutes post-captopril, one dose of immediate-release nifedipine 5 mg was given as rescue via the bite and swallow method and repeated, if necessary, in 15 minutes. The main outcome measure was SBP 30 minutes following captopril administration at initial AD episode.
RESULTS: A total of 33 AD episodes were documented, of which 18 episodes in 5 patients were treated with drug therapy. Captopril alone was effective in 4 out of 5 initial episodes (80%). Mean SBPs at baseline and 30 minutes post-captopril were 178 ± 18 mm Hg and 133 ± 28 mm Hg, respectively. There were no cases of reactive hypotension. The addition of nifedipine successfully reduced SBP in the remaining patient. Of the combined 18 initial and repeat AD episodes, 94% were successfully treated with our protocol.
CONCLUSION: Captopril appears to be safe and effective for AD management.

161E. National survey of the use of anticonvulsant prophylaxis after aneurysmal subarachnoid hemorrhage. *Denise H. Rhoney, Pharm.D.,* William M. Coplin, M.D., Sandra S. Johnson, R.N., Robert R. Johnson, II, M.D., Ross D. Zafonte, D.O., Steven R. Levine, M.D.; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: There is no evidence indicating the need for antiepileptic drug (AED) prophylaxis after aneurysmal subarachnoid hemorrhage (SAH). With clinicians left to extrapolate from other scenarios, we hypothesized there exists substantial variation in the approach to AED prophylaxis after SAH. We sought to document the present national "standard of care" and use these data to construct a clinical trial of AED prophylaxis after SAH.
METHODS: We mailed a questionnaire to United States members of the American Association of Neurological Surgeons regarding: AED prophylaxis duration, choice of AED and adverse events, and factors involved in the decision making process of offering and discontinuing AEDs after SAH.
RESULTS: Of 532 valid responses, 51.9% of respondents have university affiliations, and 98.9% have MD degrees (0.8% DO); 6.6% also have a Ph.D. General neurosurgery is practiced by 60.4%, and 12.0% primarily specialize in vascular neurosurgery. Twenty-five percent have been in practice fewer than five years, and 26.4% have been practicing more than 20 yr. Community hospitals were the primary practice site for 54.5% and university teaching hospitals for 31.0%. Thirty-five percent see fewer than 10 and 28.6% see at least 20 SAH patients per year. Thirty-eight percent claim to use a protocol for AED prophylaxis. Twenty-four percent offer AED prophylaxis for three months, and 14.8% don't regularly prescribe it; 7.7% offer it for one week.

CONCLUSIONS: There is no clear consensus regarding the rationale behind reported prescribing practices. There appears to be substantial variation regarding AED prophylaxis after SAH. A randomized, placebo-controlled trial seems justified.
Presented at the American Association of Neurological Surgeons Annual Meeting in Toronto, Ontario, Canada, April 2001.

Nutrition

162. Glutamine dependent gene expression in human monocytic cells detected by cDNA array analysis. *Gordon S. Sacks, Pharm.D.,* Katherine S. Barker, Ph.D., P. David Rogers, Pharm.D., M.S.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: Glutamine affects cell surface marker expression and function of human monocytes as well as cytokine responses in human mononuclear cells. The purpose of this study was to identify genes that are differentially expressed in human monocytes in response to lipopolysaccharide (LPS) in the presence and absence of glutamine.
METHODS: The human monocytic cell line THP-1 was passed in supplemented medium for 7 days in the presence or absence of glutamine (0.3 g/L). Cells were then exposed to medium alone or LPS (5 µg/ml) for 3 hours. RNA was extracted and [a-^{33}P] dCTP-labeled cDNA probes were prepared by reverse transcription. Probes were hybridized overnight with Research Genetics GF211 cDNA arrays at 42°C. Washed arrays were exposed to a phosphor screen for 72 hours and imaged. Statistical analysis was performed using the Chen test with 95% confidence. A two-fold difference in expression was considered significant.
RESULTS: Of 4,324 genes evaluated, 50 genes were up-regulated and 149 genes were down-regulated in THP-1 cells grown in the absence of glutamine after exposure to LPS for 3 hours compared to cells grown in the presence of glutamine. Up-regulated genes included those encoding IL-1, IL-8, protein kinase C, cyclooxygenase 1, and the IL-10 receptor. Down-regulated genes included those encoding the jun-B and jun-D proto-oncogenes, MHC class II DQ α 1, and the IL-15 receptor.
CONCLUSION: Glutamine depletion alters the expression of genes encoding immunomodulatory proteins in THP-1 cells in response to LPS. Such effects may explain the immune dysregulation associated with glutamine depletion in vivo.

163. Effect of weight loss on medication use after gastric bypass. *Laura J. Snider, Pharm.D.,* Margaret Malone, Ph.D., FCCP, Sharon A. Alger, M.D., Lyn Howard, M.B., FRCP; Albany College of Pharmacy; Albany College of Medicine, Albany, NY.

PURPOSE: To evaluate obesity related medication (ORM) changes with weight loss (TBW) following gastric bypass (GB) in patients having ≥ 75 kg (OS) or < 75 kg (US) excess body weight (EBW).
METHODS: Charts of adults undergoing GB were reviewed in an ongoing prospective study. Data were collected prior to GB and up to 48 months post GB and were stratified according to EBW. ORM were assessed at 20.1-30% and 30.1-40% TBW. Results reported as mean ± SD.
RESULTS: 217/285 study enrollees (aged 44.9 ± 9.1 years, BMI 50.5 ± 9.7 kg/m^2, 73.3% female) were prescribed ORM: OS (n=118) and US (n= 99) on 2.9 ± 1.8 and 2.7 ± 2.0 at baseline, 1.3 ± 1.1 (n=71) vs 0.9 ± 1.0 (n=42) at 20.1-30% TBW, and 1.3 ± 1.1 (n=32) vs 0.8 ± 0.9 (n= 21) after 30.1-40% TBW. At baseline, 62.7% OS vs 51.5% US were prescribed antihypertensives (HTN), 37.3% vs 31.3% analgesics (AN), 29.7% vs 23.2 % anti-diabetic agents (DB), 10.2% vs 10.3% anti-lipidemics (AL). After 20.1-30% TBW, OS and US usage was 26.8% vs 16.7% (HTN), 2.3% vs 1.4% (DB), 31.2% vs 7.0% (AN) and 1.4% vs 0% (AL). 30.1-40% TBW produced a continued gap in AN 21.9% (OS) vs 4.8% (US) and HTN 34.4% vs 9.5%.
CONCLUSIONS: ORMs decreased by 55% (OS) vs 70% (US) from pre surgery to 30.1-40% TBW. A greater decrease was observed in those least overweight at baseline which suggests that in the OS group further TBW is needed before ORM is reduced.

164E. Remaining small bowel (SB) length is longer in short bowel syndrome (SBS) patients who are able to remain off TPN after intestinal rehabilitation (IR). R.A. Nishikawa, *J.K. Siepler,* T. Diamantidis, R. Okamoto, C. Petersen; University of California, Sacramento, CA.

PURPOSE: Patients with SBS may require TPN. It has been reported that 40% of patients following IR (diet training, growth hormone, and glutamine) can wean off TPN (WPN). We intended to determine if SB length influences the ability of IR to allow patients to WPN.
METHODS: Age, wt., and SB anatomy data was collected in long-term TPN patients following IR. Patients were followed for 1 year after IR to determine if restarting TPN was required.
RESULTS: Sixteen patients participated in IR. Nine were able to WPN at the end of IR. Of those, 7 restarted TPN so that only 2 remained off TPN at the end of 1 year. The SB length was significantly longer in those remaining off TPN for 1 year compared to the other time periods.

	n (%)	age	SB length (cm/kg)
Off HPN at end of IRP	9 (57)	35 ± 11	1.8 ± 2.7
Off HPN 6 months after IRP	3 (19)	25 ± 9	3.8 ± 3.8
Off HPN 1 year after IRP	2 (13)	23 ± 10	5.4 ± 5.4*

*p<0.05

CONCLUSIONS: Patients with SBS who remained off TPN for 1 year after IR had a longer SB length than those who required restart of TPN.
Presented at the Annual Clinical Congress of the European Society of Parenteral and Enteral Nutrition, Munich, Germany, September 8-9, 2001.

Oncology

165E. Chemotherapy-induced neutropenia (CIN) and associated complications in randomized clinical trials: an evidence-based review. David C. Dale, M.D., *Gordon C. McCarter, Ph.D.,* Jeffrey Crawford, M.D., Gary H. Lyman, M.D.; University of Washington, Seattle, WA; University of California, San Francisco, CA; Duke Medical Center, Durham, NC; Albany Medical Center, Albany, NY.

PURPOSE: CIN can result in infection, hospitalization, and suboptimal chemotherapy delivery. Prophylactic G-CSF would presumably be most cost-effective in patients at high risk for neutropenic complications, but no reliable aggregate record of rates of neutropenia by disease and chemotherapy regimen currently exists. Thus, we systematically reviewed published data and tabulated reported rates of neutropenia/neutropenic sequelae in patients treated for non-Hodgkin's lymphoma (NHL) and early breast cancer (EBC).
METHODS: Randomized clinical trials with ≥50 patients/arm, published in English between 1990-2000, were reviewed.
RESULTS: Hematological toxicity reporting varied widely. 73 NHL studies met inclusion criteria; 39 provided hematologic toxicity data. Reported grade III/IV neutropenia ranged from 8%-51% following CHOP. Rates for other regimens were similarly variable. For EBC, 42 of 87 included studies contained pertinent data. Grade III/IV neutropenia/leukopenia ranged from 1%-78% with CMF, and from 3%-100% with CAF or FEC. Severe leukopenia rates of 2%-6% were reported for AC, but blood counts were obtained only on cycle day 1 and serious infections/sepsis ranged from 2.4%-3.3%, making the leukopenia rates suspect. The range of myelotoxicity rates within regimens may represent true variability, discrepant patient populations, ill-timed blood collection, or under-reporting. Reporting of chemotherapy administration changes, febrile neutropenia, infection, and hospitalization was inconsistent and widely variable.
CONCLUSION: The risk of neutropenic complications from specific chemotherapy regimens may not be assessable from the current literature, given the lack of standardized reporting methods. Efforts to better guide cost-effective use of G-CSF should focus on identifying risk factors that reliably predict neutropenic complications in individual patients.
Presented at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001.

166E. Prophylaxis of chemotherapy-induced neutropenia (CIN) with a once-per-cycle dose of pegfilgrastim is equivalent to daily filgrastim in high-risk breast cancer (BC) patients. Frankie A. Holmes, M.D., J. O'Shaughnessy, S. Vukelja, *Bertrand C. Liang*; US Oncology, Houston, TX; Oncology Hematology Association, Pittsburgh, PA; University of California at Los Angeles Medical Center, Los Angeles, CA; Georgia Cancer Specialists, Decatur, GA; Southwest Oncology Associates, Lafayette, LA; Hematology/Oncology Midwest Cancer Research Group, Northfield, IL; Amgen Inc., Thousand Oaks, CA.

PURPOSE: Neutropenia, a major toxicity of chemotherapy, places patients at risk of serious complications, including infection and suboptimal chemotherapy dose delivery. A randomized, double-blind phase 3 trial compared once-per-cycle prophylaxis with a single dose of sustained-duration pegfilgrastim to daily filgrastim for reducing CIN in high-risk BC patients.
METHODS: 310 patients with stage II-IV BC from 62 centers receiving 4 cycles of doxorubicin/docetaxel were randomized to a single dose (100 µg/kg) of pegfilgrastim (with daily placebo) or to daily filgrastim (5µg/kg/d) until ANC ≥10 x 10^9/L or for 14 d, starting 24-hr post-chemotherapy. The primary endpoint was duration of severe neutropenia (DSN, days with ANC <0.5 x 10^9/L).
RESULTS: Group demographics were similar. In patients treated per protocol, mean DSN was 1.7 days with pegfilgrastim (n=131) and 1.6 days with filgrastim (n=129), with 95% CI for difference in means of -0.23 to 0.40 days. The incidence of SN was 76% in cycle 1 for both groups, with comparable ANC nadirs. In cycles 2-4, trends towards reduced SN favored pegfilgrastim. Febrile neutropenia (temp. >38.2° with SN) over all cycles was reduced 50% with pegfilgrastim (9% vs 18% for filgrastim, p=0.0275). Side effects, including bone pain, were similar for both groups.
CONCLUSIONS: A once-per-cycle dose of prophylactic pegfilgrastim is at least as effective as daily filgrastim injections in reducing the risk of neutropenia, and is similarly will tolerated. Once-per-cycle administration enhances patient compliance and may better serve health care professionals and patients.

Presented at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001.

167E. Fixed-dose, once-per-cycle pegfilgrastim is equivalent to daily filgrastim as prophylaxis against chemotherapy-induced neutropenia (CIN) in high-risk breast cancer patients. M. Green, H. Koelbl, J. Baselga, E. Kubista, V. Guillem, P. Gascon, S. Siena, R. Lalisang, P. Krippl, M. Clemens, V. Zani, S. Bachir, J. Renwick, *Bertrand C. Liang,* M. Piccart; RMH, Melbourne, Australia; University-Klinik, Halle, Germany; H. Vall d'Hebron, Barcelona, Spain; AKH, Wien, Austria; IVO, Valencia, Spain; H Clinic I Prov, Barcelona, Spain; Ospedale Niguarda Ca Granda, Milan, Italy; AZM, Maastricht, NL; University-Klinikum, Graz, Austria; KMB, Trier, Germany; Amgen Inc., Thousand Oaks, CA; Inst. J. Bordet, Brussels, Belgium.

PURPOSE: Prophylactic Filgrastim reduces the incidence and duration of CIN, thereby decreasing the risks of infection and compromised outcomes due to suboptimal chemotherapy delivery. Pegfilgrastim is a novel sustained-duration cytokine with individualized self-regulating pharmacokinetics created by attaching polyethylene glycol to Filgrastim. This randomized, blinded phase 3 trial compared a once-per-cycle single 6-mg fixed dose of pegfilgrastim to daily Filgrastim as CIN prophylaxis in high-risk breast cancer patients.
METHODS: 157 stage II-IV breast cancer patients receiving doxorubicin/docetaxel at 35 centers internationally were randomized to a single 6-mg dose of pegfilgrastim (with daily placebo), or daily Filgrastim (5 µg/kg/d), from 24-hr post-chemotherapy until ANC ≥10 x 10^9/L or for 14d. The primary outcome was duration of severe neutropenia (DSN, days with ANC <0.5 x 10^9/L).
RESULTS: In patients treated per protocol, the incidence of SN was 82% with pegfilgrastim (n=68) and 84% with Filgrastim (n=62); mean DSN was 1.8 and 1.6 days, respectively. Efficacy in each group was similar for all body weights. The incidence of febrile neutropenia was 13% for pegfilgrastim, 20% for Filgrastim. Delivered chemotherapy dose was comparable; 5% of patients experienced a ≥ 25% dose reduction in any cycle. Side effects, including bone pain, were similar for both groups.
CONCLUSIONS: A single once-per-cycle 6-mg fixed dose of pegfilgrastim is at least as effective as daily filgrastim injections for prophylaxis against CIN, and is similarly well tolerated. Once-per-cycle, fixed-dose pegfilgrastim has the potential to simplify the management of CIN for health care professionals and patients.
Presented at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001.

168. Risk factors that influence mortality among hospitalized patients with neutropenic fever. *Renee C. Cox, R.Ph., Pharm.D. candidate,* Jane Pruemer, Pharm.D., Monica Kopp, R.Ph., Jeff Guo, Ph.D.; University of Cincinnati; The University Hospital; VA Medical Center; Cincinnati, OH.

BACKGROUND: Despite advances in medical practice, the mortality associated with neutropenic fever in the adult cancer population remains 6%-30%[1]. For high-risk patients, hospitalization is appropriate, since the close medical surveillance and ready availability of emergency care in the hospital could prove crucial for rapidly deteriorating patients. Identification of these high-risk patients is imperative. Differentiation of high risk versus low risk patients may help to decrease costs, free inpatient beds, and allows patients to enjoy a familiar home environment.
OBJECTIVE: Identify risk factors that influence mortality in neutropenic fever patients at a 400-bed teaching hospital. Determine the mortality rate in this group of patients.
METHODS: Retrospective chart review of ninety patients who where hospitalized with neutropenic fever at a 400-bed teaching hospital from January 1999 through December 2000. Data collected included age, sex, race, type of cancer, chemotherapy, temperature, ANC at presentation, ANC (absolute neutrophil count) nadir, duration ANC <500/mm^3, albumin, CSF (colony stimulating factor) use, positive cultures, positive blood cultures, death.
RESULTS: Age, use of CSFs, and presence of positive blood cultures were the only factors found to correlate with mortality ($p<0.05$). The mortality rate in this population was 7%.
CONCLUSION: When attempting to identify high-risk patients with neutropenic fever, age, use of CSFs and presence of positive blood cultures must be considered. The mortality rate at this institution falls within previously reported values.

169. Evaluation of the irinotecan metabolizing enzyme in tumors using tissue arrays. *Margaret K. Ma, Pharm.D.,* Wanghai Zhang, M.D., Ph.D., Guang Xu, M.D., Ph.D., Howard L. McLeod, Pharm.D.; Washington University, St. Louis, MO.

PURPOSE: Irinotecan, which has demonstrated activity against a number of solid tumors, requires bioactivation by carboxylesterases (CES) to its active metabolite SN-38 for anti-tumor activity. Recently, purified human liver enzyme CES2 was demonstrated to be the primary carboxylesterase isoform for irinotecan bioactivation at pharmacologically achievable drug concentrations. However, CES expression is not only localized in the liver. Local SN-38 production by tumor tissue CES was also described. Thus, an evaluation of CES2 expression in tissue arrays was performed.
METHODS: The expression and activity of CES2 was determined using western blotting and HPLC in 13 human liver samples. The distribution of CES2 was evaluated in 154 cancer tissues using immunohistochemistry.
RESULTS: SN-38 production was 5- to 35-fold greater in the microsomal than cytosolic fractions. A significant correlation was found between SN-38 production and CES2 protein concentration in the liver microsomes (R^s=0.65; p=0.01). CES2 tumor expression was localized to the cytoplasm and varied significantly among 154 cancer tissues from 18 human tumor types; 11/18 had moderate to intense positive, 5/18 were weakly positive and 2/18 tumor types were negative for CES2 staining, respectively.
CONCLUSION: Our study provides further evidence of an important role for microsomal CES2 in irinotecan activation. Tumor CES2 expression may prospectively aid prediction of irinotecan activity and provide guidance for the better use of this agent to treat specific tumor types. In addition, studies integrating all drug-metabolizing enzymes in the irinotecan pathway are ongoing to provide a more comprehensive strategy for irinotecan activation, efficacy and/or toxicity.

170. Sustained-duration, once-per-chemotherapy-cycle pegfilgrastim demonstrates highly efficient, self-regulating, neutrophil-dependent elimination. *Sally L. Yowell, Pharm.D.,* Jeffrey Crawford, M.D., Frankie Ann Holmes, M.D., Bing-Bing Yang, Ph.D., Bertrand C. Liang, M.D.; Duke University, Durham, NC; Texas Oncology, PA, Dallas, TX; Amgen, Inc, Thousand Oaks, CA.

PURPOSE: Pegfilgrastim is a sustained-duration formulation of filgrastim (G-CSF) under investigation for single-dose-per-cycle treatment of chemotherapy-induced neutropenia. Dose-finding phase I/II clinical trials were conducted in cancer patients to assess the pharmacokinetics of pegfilgrastim given after chemotherapy.
METHODS: In a phase I/II trial, 10 NSCLC patients received a single dose of pegfilgrastim at 30, 100, or 300 µg/kg, 24 hours after carboplatin/paclitaxel cycle 1. In a phase II trial, 129 breast cancer patients received a single dose of pegfilgrastim at 30, 60, or 100 µg/kg 24 hours after docetaxel/doxorubicin cycle 1. Serum samples were evaluated with a validated ELISA for serum cytokine concentration.
RESULTS: The PK of pegfilgrastim were non-linear (medians presented). In NSCLC, C_{max} at 30 µg/kg was 7.2 ng/ml; AUC, 734 ng/h/ml; clearance, 40.9 ml/h/kg. At 300 µg/kg, C_{max} was 945 ng/ml; AUC, 137229 ng/h/ml; clearance, 2.19 ml/h/kg. In breast cancer, C_{max} at 30 µg/kg was 15 ng/ml; AUC, 1136.2 ng/h/ml; clearance, 26.4 ml/h/kg. At 100 µg/kg, C_{max} was 174.7 ng/ml; AUC, 14961.4 ng/h/ml; clearance 6.7 ml/h/kg. Serum clearance decreased with increasing dose, resulting in non-linear increases in C_{max} and AUC. PK were also dependent on ANC; serum concentrations remained elevated during neutropenia, but rapidly declined during ANC recovery post chemotherapy nadir, suggesting saturable neutrophil-mediated elimination.
CONCLUSIONS: Pegfilgrastim demonstrates saturable, self-regulated, neutrophil-mediated clearance when administered as a once-per-cycle dose following chemotherapy. This mechanism may enhance risk reduction in individual patients by decreasing the impact of patient and therapy differences that result in varying durations of neutropenia.

171E. Population pharmacokinetics of tacrolimus following hematopoietic stem cell transplantation. *Pamala A. Jacobson, Pharm.D.,* Juki W. Ng, Pharm.D., Voravit Ratanatharathorn, M.D., Joseph P Uberti, M.D., Richard C. Brundage, Pharm.D., Ph.D.; University of Minnesota, Minneapolis, MN, University of Michigan, Ann Arbor, MI.

PURPOSE: Tacrolimus is an effective agent in the prevention of graft vs host disease (GVHD). Unfortunately, tacrolimus is associated with significant nephrotoxicity and neurotoxicity. Toxicity is reduced when blood concentrations are maintained at concentrations ≤15 ng/ml. The goal was to determine the population pharmacokinetics of tacrolimus using nonlinear mixed-effect modeling (NONMEM) and create a model to predict tacrolimus concentrations.
METHODS: Steady-state whole blood tacrolimus concentrations (n=1625) were obtained in 122 adult patients during routine clinical care between days 1 and 122 post transplant. Patients initially received tacrolimus by IV continuous infusion and were converted to PO therapy as tolerated.
RESULTS: Population estimate of CL was 5.22 L/hr and F was 0.28. Forward inclusion/backward elimination was used to build a regression model for CL and F with common clinical covariates. No covariates tested were predictive of oral F. CL was reduced by rises in total bilirubin and SCr, and the presence of GVHD or VOD. The final CL model was:

CL (L/hr)=5.22 * (any of the following relevant covariates)
0.797 if bilirubin 2-9.9 mg/dl or 0.581 if bilirubin > 10 mg/dl
0.587 if SCr > 2 mg/dl
0.814 if grade III-IV GVHD present
0.814 if VOD present

The inter-individual variability in CL and F was 33% and 44%, respectively.
CONCLUSION: The dose required to achieve a given Css may be estimated using the predicted CL. Dose adjustments made with this model may improve

the accuracy of target-controlled tacrolimus therapy and reduce toxicity.
Presented at the 42nd Annual Meeting of the American Society of Hematology, San Francisco, CA, December 2000.

172. Effects of ifosfamide and carboplatin therapy on glomerular filtration rate in children and young adults. *Kristine R. Crews, Pharm.D.,* David Gregornik, Pharm.D., William R. Crom, Pharm.D., Charles B. Pratt, M.D., William H. Meyer, M.D., John H. Rodman, Pharm.D.; St. Jude Children's Research Hospital, Memphis, TN.

PURPOSE: The combination of ifosfamide (I) and carboplatin (C), while effective against pediatric solid tumors, is potentially nephrotoxic. This study evaluated the cumulative effects of multiple courses of I and C on glomerular filtration rates (GFR) in pediatric and young adult patients with osteosarcoma. Because methotrexate (MTX) is extensively eliminated by the kidneys, we also investigated the relationship between GFR and MTX systemic clearance in this patient population.
METHODS: Fifty-seven newly diagnosed osteosarcoma patients received 4 courses of I 2.65 g/m^2 IV x 3 days with C 560 mg/m^2 IV on day 1. In addition, patients received 9 courses of high-dose MTX 12 g/m^2 concurrent with I + C. GFR was determined by ^{99m}Tc-DTPA serum clearance (Tc Cl) prior to treatment (n=56); at week 20, after MTX course 3 and before I + C course 4 (n= 47); and at week 35, after MTX course 9 (n= 40). Median age at enrollment was 14.1 years (range, 5.8 to 24.1 years); 32 patients (56%) were male.
RESULTS: Normalized GFR ranged from 102 to 253 ml/min/1.73 m^2 with a mean value of 150 ml/min/1.73 m^2 prior to therapy. There was a significant decrease in mean GFR values over the course of the study (ANOVA, $p<0.01$) to 130 ml/min/1.73 m^2 at week 20 (prior to I + C course 4), and 121 ml/min/1.73 m^2 at week 35. GFR values obtained at week 20 were significantly correlated ($p<0.05$) with course 3 (week 16) MTX clearances (linear regression, $r^2=0.12$) and GFR values at week 35 were significantly correlated with course 9 (week 34) MTX clearances (linear regression, $r^2=0.20$).
CONCLUSIONS: Cumulative doses of I and C are associated with a decrease in GFR, as measured by Tc Cl, in this population of children and young adults. GFR is significantly correlated with MTX clearance. Decreased GFR may predict delayed MTX clearance, which in turn may represent an increased risk for toxicity. Supported by NIH grants CA21765 and CA23099 and ALSAC.

Pediatrics

173. The pharmacokinetics of cerivastatin in pediatric subjects. *Evan A. Stein,* Prabhu Rajagopalan, Arthur L. Mazzu; Metabolic and Atherosclerosis Research Center, Cincinnati, OH; Bayer Corporation, West Haven, CT.

BACKGROUND: Statins are the drug of choice for the treatment of familial hypercholesterolemia, an inherited disorder with very early onset of coronary heart disease and present in childhood.
OBJECTIVE: To examine the pharmacokinetic parameters (PK) of cerivastatin 0.4 mg and lipid parameters in a pediatric population.
METHODS: Children (age 10-13 years, 4M and 3F, mean body weight 62.8 kg) and adolescents (age 14-17, 5M and 5F, mean body weight 59.6 kg) were administered cerivastatin 0.4 mg QD for 7 days. PK were measured on day 7 from a 24-hr concentration profile. Lipid parameters were measured on days 1 and 8.
RESULTS:

Parameter	Age Group*			
	10-13 Years		14-17 Years	
	CER	M23	CER	M23
n	7	7	10	9
$AUC_{0\text{-}tn,}$ µg.hr/L	22.3 (29)	3.59 (56)	24.9 (48)	3.53 (78)
$C_{max,}$ µg/L	4.77 (32)	0.58 (39)	5.11 (42)	0.59 (36)
$t_{max,}$ hr	1.8 (40)	3.9 (23)	1.9 (45)	3.9 (34)
$t_{1/2,}$ hr	2.7 (18)	ND	3.6 (40)	ND

*geometric mean (%CV); ND=not determined; tn=last measurable concentration; M1 metabolite concentrations were insufficient for accurate assessment

After just 7 days of treatment, cerivastatin 0.4 mg reduced LDL-C and total-C by 24.7% and 19.6%, respectively. Cerivastatin 0.4 mg was well tolerated in all patients.
CONCLUSION: Pharmacokinetics of cerivastatin 0.4 mg in children are consistent with those observed in adults, indicating that cerivastatin can be used in pediatric patients without concern for dose alterations. The 7-day pharmacodynamic effect of cerivastatin 0.4 mg indicates a rapid onset of the lipid-lowering effect and suggests substantially greater LDL-C reductions will be attained by 2 weeks, the time when 90% of LDL-C reductions are usually seen in adults.

174. An assessment of patient or caregiver baseline knowledge of asthma. *Paul J. Munzenberger, Pharm.D.,* Abdul H. Bahrainwala, M.D., Kerry L. Tedesco; Wayne State University, Detroit, MI.

PURPOSE: This study documented patient or caregiver knowledge of asthma to determine overall educational needs at the initial visit.
METHODS: At their initial visit to a pediatric asthma specialist, patients or caregivers (child < 12 y/o), referred from primary care, completed a knowledge assessment survey regarding asthma physiologic characteristics, triggers, symptoms and warning signs, and medical management. Asthma severity and adherence with NHLBI treatment guidelines were also determined.
RESULTS: Seventy-eight assessment surveys were completed; 62 by caregivers and 16 by older children. Seventeen, 42, and 17 patients had mild, moderate, and severe persistent asthma, respectively. Overall adherence with NHLBI treatment guidelines was 34.3 %. Mean scores on the recognition of physiologic characteristics, triggers, and symptoms and signs were 70, 85, and 82 percent, respectively. Inflammation was identified as a characteristic by 75%. Patient specific triggers and symptoms/warning signs were identified by 88 and 89 percent, respectively. Eighty-six percent identified albuterol or pirbuterol as their rescue medication. However, only 56% knew how long it would take for a response following their administration. Inhaled steroids were considered a rescue medication, either alone or in addition to albuterol or pirbuterol, by 32%. Only forty percent identified all their controller medication. Seventy-five percent of patients prescribed inhaled steroids identified them as controller drugs. Albuterol or pirbuterol and inhaled steroids were selected as the drug to use just prior to exercise in 63 and 24 percent, respectively.
CONCLUSION: Patient knowledge of drug use was the weakest area and should be addresses within patient education programs.

175. Musical perception cry analysis for monitoring the effect of topical anesthesia during circumcision. *Victoria Tutag-Lehr, Pharm.D.,* Nathan W. Montgomery, B.A., Jacob V. Aranda, M.D., Ph.D.; Children's Hospital of Michigan/Wayne State University at Detroit, Detroit, MI; NWM Technologies, LLC, Royal Oak, MI.

PURPOSE: To determine whether a new method of cry analysis by 3-dimensional power spectrum and musical perception is useful as quantitative marker of pain for infants using the newborn male circumcision model.
METHODS: The cries of eight newborn males were recorded by professional grade recording systems during circumcision using the Gomco clamp and dorsal penile nerve block. Sounds were analyzed using an audio editor. Musical perception was used to identify and assess variables in cry responses throughout the procedure. A musical notation program was used to display the sound data in musical notation. Data were displayed as wave representation for visual examination of sound type, duration, peak amplitude, pitch and other characteristics. Technological advances in sound recording and analysis allowed definitions of cry characteristics not previously possible.
RESULTS: Recorded cries from eight newborn males were assessed using a 3-dimensional power spectrum (duration, amplitude, pitch). Recording time ranged from 7.13 to 11.20 minutes. Cry, gasps, breath, and dysphonations were the most frequent responses. Cry amplitude ranged from –28.6 dB to 0.0 dB, and pitch from 352 Hz to 1267 Hz. Highest values occurred during foreskin separation and clamp application, which have been documented as the most painful events. Variables included duration, attack (suddenness of sound onset), decay, rhythm, and spectral harmonic content.
CONCLUSION: Infant cry analyzed using musical perception and 3 dimensional power spectrum is a potentially useful marker of infant pain response and a tool for neonatal pain assessment in clinical trials.

176. Pharmacokinetics of a new nifedipine suspension in young adults. *Kim G. Adcock, Pharm.D.,* John Rowell, MSN, Tim O. Davis, B.S., Virginia Johnson, M.S., Jivn-Ren Chen, Ph.D., John T. Wilson, M.D.; Louisiana State University Health Sciences Center at Shreveport; Sage Pharmaceuticals, Inc, Shreveport, LA.

PURPOSE: Nifedipine, a calcium channel blocker, has been used in children for the treatment of hypertension for 15 years despite a lack of pharmacokinetic data and a pediatric formulation. Currently, the nifedipine liquid filled capsule is used to dose infants and children, with a risk of inaccurate dosing. A nifedipine suspension was developed to overcome this problem. Pharmacokinetic parameters for this formulation were evaluated prior to its study in children.
METHODS: A single-blind, randomized, two-week crossover, standard-controlled, single oral dose study of the nifedipine suspension was conducted in healthy male adults (ages 18-36 years). A single 10 mg dose of nifedipine administered as the suspension or capsule (Procardia®) was followed by blood sampling for a 24-hour period. Safety estimates included blood pressure and heart rate. The pharmacokinetic parameters analyzed included area under the curve (AUC), maximum concentration (Cmax), time of maximum concentration (Tmax), elimination rate constant (Kel), and half-life (T1/2).
RESULTS: Eighteen of 20 subjects completed the study. Pharmacokinetic parameters for the nifedipine suspension included AUC 8073 ng•min/ml, Cmax 89 ng/ml, Tmax 24 min, Kel 0.007 min^{-1}, and T1/2 98 minutes. Inspection revealed a similar nifedipine concentration range for Cmax and average concentration/time profiles for both preparations. No patient

experienced a clinically significant change in blood pressure or heart rate.
CONCLUSIONS: The pharmacokinetic profile of the new nifedipine suspension appears similar to that of the immediate release nifedipine capsule. Pharmacokinetic characteristics of this new nifedipine formulation allow its evaluation in children. (Supported by NIH Grant # UOI HD31315)

177. Impact of a pharmacy educational program on pediatric patients with seizures. *Kimberly Tallian, Pharm.D.,* Ragie Aboulhosn, Pharm.D. candidate, Pradeep Gidwani, M.D., M.P.H., William Lewis, M.D., David Haller, Pharm.D.; Children's Hospital, San Diego, CA.

PURPOSE: Concern about the preventability of adverse drug events (ADEs) and medication errors, especially in the pediatric population, is increasing. Programs targeting the most common classes of ADEs are needed. Based on a retrospective review at our institution of all ADEs spontaneously reported between 1997 and 2000, anticonvulsants accounted for 10.4% of ADEs of which 39.7% were considered preventable due a lack of consistent parent/patient education.
METHODS: We designed a study to evaluate the parent's knowledge at baseline and following a comprehensive educational program provided by a pharmacist regarding their child's anticonvulsant medications with respect to dose, adverse effects, and storage. Parents were also surveyed at baseline and post education regarding their satisfaction with the information provided by all healthcare professionals as well as the amount of information the parent knew about proper seizure first aid and precautions. All new and return parents of seizure patients were included in the study.
RESULTS: Seventy parent's knowledge improved following the educational program provided by a pharmacist. Knowledge of anticonvulsant adverse effects, adverse event management, seizure first aid, medication storage, and seizure precaution for pre versus post pharmacist consultation improved from 0.134 to 0.926 ($p<0.001$), 0.478 to 1.00 ($p<0.001$), 0.217 to 1.00 ($p<0.001$), 0.550 to 0.986 ($p<0.001$), and 0.289 to 0.957 ($p<0.001$), respectively. All parents were also highly satisfied with the role of the pharmacist (1.97 to 3.69 ($p<0.0001$)).
CONCLUSION: The pharmacist is perceived by the parents to be a valuable medication education resource. Pharmacists can plays an important role in the multidisciplinary approach to the management of pediatric patients with seizures.

178E. Efficacy and complications of sirolimus in pediatric renal transplant recipients. *Lonnie D. Smith, Pharm.D.,* K. Troy Somerville, Pharm.D., Cecile Aguayo, BSN, Joe Sherbotie M.D.; University of Utah Hospital, Salt Lake City, UT.

BACKGROUND: Sirolimus (SRL) has proven efficacious in the prevention of renal allograft rejection in adult recipients. Limited data in the pediatric population exists. We report our early experience with SRL in pediatric renal transplant recipients.
METHODS: From 4/00 to 1/01 SRL was initiated in 13 pediatric renal transplant recipients. Prior to SRL initiation 8 patients were maintained on tacrolimus (TAC) + prednisone (PRED) + mycophenolate mofetil (MMF), 2 patients on TAC + PRED, 1 patient on cyclosporine (CYA) + PRED, 1 patient on TAC + MMF, and 1 patient with DGF and acute TAC toxicity on thymoglobulin + PRED. Follow-up ranged from 1 to 10 months. SRL was dosed to achieve a target trough of 8-12 ng/ml.
RESULTS: Mean age 14 years; 9 male, 4 female; donor source: 10 CAD, 3 LRD. Reasons for starting SRL included: Steroid-resistant acute rejection related to noncompliance (ARNC) in 3/13, MMF intolerance (GI, leukopenia) in 5/13, acute rejection without noncompliance (AR) in 3/13, delayed graft function with biopsy proven acute TAC toxicity (DGF/TAC) in 1/13, and TAC toxicity in 1 of 13 patients. Serum creatinine stabilized or decreased in all three patients with ARNC and one of these patients subsequently experienced a steroid-responsive AR with subtherapeutic SRL and TAC. All patients with AR and one with DGF/TAC had improved function. All 5 patients with MMF intolerance had resolution of side effects, with stable graft function after SRL. The patient with TAC toxicity had improved graft function. Adverse effects associated with SRL included thrombocytopenia (5/13), decrease in HCT (4/13), elevated cholesterol (6/13), elevated triglycerides (8/13) and oral ulcers (4/13). Recommended dosing of SRL (6 mg-load with 2 mg-maintenance) resulted in subtherapeutic levels in the first 2 patients. Subsequently, SRL doses were changed to achieve target trough levels. The overall mean loading dose and maintenance dose used was 11 mg/m^2 and 4.2 mg/m^2, respectively.
CONCLUSION: SRL provides safe and effective immunosuppression in pediatric renal transplant recipients. Pediatric renal transplant patients may require higher than recommended SRL doses to maintain target trough levels.
Presented at the 12th Congress of the International Pediatric Nephrology Association, Seattle, WA, September 1-5, 2001.

179E. A randomized, multicenter study of the safety and efficacy of remifentanil versus halothane in neonates undergoing surgery for pyloric stenosis. *Lynn G. Henson, Pharm.D.,* Richard H. Blum, M.D., Jeffrey L. Galinkin, M.D., C. Dean Kurth, M.D., Francis X. McGowan, M.D., Peter J. Davis, M.D.; GlaxoSmithKline Inc., Research Triangle Park, NC; The Children's Hospital, Boston, MA; Children's Hospital of Philadelphia, Philadelphia, PA; Children's Hospital of Pittsburgh, Pittsburgh, PA.

PURPOSE: This study compared the emergence and recovery profiles, response to surgical stress, and safety of remifentanil and halothane when administered as part of a balanced anesthetic technique for neonates and infants undergoing pyloromyotomy.
METHODS: This open-label, parallel group active control study compared remifentanil 0.4 µg/kg/min + 70% nitrous oxide/30% oxygen and halothane 0.4% end-tidal concentration + 70% nitrous oxide/30% oxygen in full-term (≥37 weeks) neonates and infants (≤8 weeks). Specific criteria were used to define inadequate anesthesia. Remifentanil subjects were treated with a supplemental bolus (1 µg/kg) ± a 50% increase in infusion rate. The halothane group was treated by increasing end-tidal concentration in 0.4% increments. Hemodynamic and respiratory parameters, PACU discharge time and recovery scores were assessed. Prior to surgery and for a maximum of 12 hours after, pneumocardiograms were recorded and analyzed (blinded).
RESULTS: Sixty subjects were enrolled. No significant adverse effects were directly related to the study drugs, or statistical differences between recovery and discharge parameters. Initial quality of recovery was higher in the remifentanil group ($p<0.004$) but not statistically different at later times. Most subjects required remifentanil (71%) or halothane (82%) dosage adjustments to treat light anesthesia. Dosage adjustments for excessive anesthesia were greater in the halothane group (32%) versus remifentanil group (11%). No subjects required naloxone.
CONCLUSION: The hemodynamic, emergence and recovery profiles were similar for subjects in both treatment groups. Overall, remifentanil appeared to be well tolerated, was associated with rapid recovery, and was without evidence of respiratory depression in neonates and infants undergoing surgery for pyloric stenosis.
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180. Magnesium sulfate administered via continuous intravenous infusion in pediatric patients with refractory status asthmaticus. *Mark L. Glover, Pharm.D.,* Cary Machado, Pharm.D., Balagangadhar Totapally, M.D.; Nova Southeastern University, Ft. Lauderdale, FL; Miami Children's Hospital, Miami, FL.

PURPOSE: To evaluate the dosing and safety of intravenous magnesium sulfate administered via continuous infusion for refractory status asthmaticus.
METHODS: All patients admitted to the pediatric intensive care unit (PICU) between January 1998 and March 2001 who were prescribed magnesium sulfate via continuous infusion were identified by reviewing PICU patient profiles. The medical history, demographic data, vital signs, magnesium dosing history, and concurrent medications of the patients were recorded.
RESULTS: Forty PICU patients represent our study population. The mean age was 82.6 ± 64.6 months; eighteen patients were male. The mean magnesium loading dose (mg/kg) was 29.6 ± 13.2 with a mean infusion dose (mg/kg/hr) of 18.4 ± 6.5 with a significant difference in dosing noted between patients weighing less than 30 kg (LW) and those with a higher weight (HW). The mean magnesium loading dose (mg/kg) in the LW group was 35.3 ± 12.7 compared to 21.9 ± 9.9 in the HW group ($p<0.05$). Further, the mean infusion doses (mg/kg/hr) of the two groups were 21.6 ± 6 and 14.6 ± 4.2, respectively ($p<0.05$). There was no significant difference between the mean concentrations (mg/dl) reported between the two groups (LW 3.9 ± 0.6; HW 3.6 ± 0.5). All patients were prescribed nebulized albuterol, ipratropium, and intravenous methylprednisolone prior to magnesium therapy. Aminophylline and ketamine were prescribed to twenty-eight and four patients, respectively. No cardiovascular adverse effects were noted during magnesium therapy.
CONCLUSION: Intravenous magnesium sulfate administered via continuous infusion to refractory status asthmaticus patients represents a safe mode of drug delivery.

181. Intravenous fat emulsion in neonates receiving extracorporeal membrane oxygenation. *Marcia L. Buck, Pharm.D., FCCP,* Roberta A. Ksenich, RNC, Peggy Wooldridge, RN, M. Pamela Griffin, M.D.; University of Virginia Children's Medical Center, Charlottesville, VA.

PURPOSE: Previous *in vitro* work has shown that infusion of fat emulsion into extracorporeal membrane oxygenation (ECMO) circuits results in accumulation and increased clotting. This study compared the effects of infusing fat emulsion through the circuit to infusion through separate venous access.
METHODS: A prospective, randomized open-label trial was conducted over 3 years. Neonates receiving ECMO who required intravenous nutrition were eligible. Infants with active bleeding or who were at high risk for hemorrhage were excluded. Patients received 1-3 gram/kg/day fat emulsion into either the ECMO circuit or separate venous access. The circuit and samples of blood were evaluated hourly for phase separation (breaking of the emulsion), layering out of the emulsion from the blood, and clots. After completion, the oxygenators were dissected and examined.
RESULTS: Nine neonates completed the protocol. The demographics of the groups were similar, except for a slightly faster infusion rate in the venous group (1.08 ± 0.87 versus 0.72 ± 0.24 ml/hr). Of the four venous access patients, two developed clots in the circuit despite adequate anticoagulation. One also had layering out of the emulsion. In the five circuit patients, two

had layering out and four had clots. No cases of phase separation occurred.
CONCLUSION: Although both methods were associated with layering out and clot formation, these effects were observed more frequently with administration into the circuit, particularly in areas of stasis. This may result in impaired delivery of calories and adversely affect circuit integrity. It is recommended that fat emulsion be administered through separate venous access during ECMO.

Pharmacoeconomics

182. Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. *C.A. Bond, Pharm.D., FASHP, FCCP,* Cynthia L. Raehl, Pharm.D., FASHP, FCCP, Todd Franke, Ph.D.; Texas Tech University Health Sciences Center at Amarillo, Amarillo, TX; University of California at Los Angeles, Los Angeles, CA.

This study evaluated the direct relationships and associations between clinical pharmacy services, pharmacist staffing, and medication errors in United States hospitals. A database was constructed from the 1992 American Hospital Association's Abridged Guide to the Health Care Field and the 1992 National Clinical Pharmacy Services Database. Both simple and multiple regression analysis were employed to determine the relationships and associations.
A total of 429,827 medication errors were evaluated from 1081 hospitals (study population). Medication errors occurred in 5.22% of the patients admitted to these hospitals each year. Each hospital experienced a medication error every 22.04 hours (every 19.13 admissions). Factors associated with increased medication errors per occupied bed per year were: drug-use evaluation (slope 0.0023476, p=0.006), the number of hospital pharmacy administrators per occupied bed (slope 29.1972932, p<0.001), and the number of dispensing pharmacists per occupied bed (slope 19.3784148, p<0.001). Factors associated with decreased medication errors per occupied bed per year were: a drug information service (slope -0.1279301, p<0.001), pharmacist provided adverse drug reaction management (slope -0.3409332, p<0.001), pharmacist provided drug protocol management (slope -0.3981472, p=0.013), medical rounds participation (slope -0.6974303, p<0.001), pharmacist provided admission histories (slope -1.6021493, p<0.001), and the number of clinical pharmacists per occupied bed (slope -9.5483813, p<0.001).
Clinical pharmacy services and hospital pharmacy staffing were associated with medication error rates in U.S. hospitals. The results of this study should help hospitals reduce the number of medication errors that occur each year.

183. Financial assessment of samples dispensed at a family medicine residency program (FMRP). *David M. Hachey, Pharm.D.,* Rex W. Force, Pharm.D., FCCP, BCPS, Wendy Force, R.Ph., Julie M. Johnson, Pharm.D., Melanie Sadler, Pharm.D.; Idaho State University, Pocatello, ID.

PURPOSE: To assess the financial aspects of sample medications dispensed at a FMRP.
METHODS: In response to JCAHO regulations, a secure sample dispensing system was developed at a FMRP to replace one maintained by nurses, physicians and pharmaceutical representatives. Written prescriptions for samples were presented and filled by pharmacists in a manner similar to retail pharmacy with printed labels. Pharmacists provided instructions and counseling while maintaining a computerized database (FileMaker Pro™) of samples and patient profiles. Medications were organized in the database by therapeutic category and a daily inventory was printed for physicians, nurses and pharmaceutical representatives. Clinic data were evaluated for patient and employee utilization over an 8-month period using the database. Value per sample prescription dispensed was based on prices at www.drugstore.com (as of 6/1/2001).
RESULTS: Over the study period, there were 9866 patient visits. 628 patients received a total of 1177 sample prescriptions. An average of 7 patient sample prescriptions were processed per day for an 8-month total value of $72,194.60, or $61.33 per prescription. The 5 most frequently processed medication classes were antidepressants (19%), antihistamines (11%), NSAIDs (11%), antibiotics (8%) and proton pump inhibitors (8%). Sixty-eight percent (33/48) of employees had 113 prescriptions processed for themselves or a family member, which accounted for almost 9% of all sample prescriptions processed. Total value for employees was $4105.47, or $36.33 per sample dispensed.
CONCLUSION: Over the 8-month study period, our clinic processed a total of 1290 sample prescriptions valued at $76,300.07 for patients and employees.

184. Documentation of clinical pharmacy interactions with infectious diseases (ID) consult service. Amanda L. Hastings, Pharm.D., *Jeffrey J. Kuper, Pharm.D., BCPS,* Joseph F. John, M.D.; Rutgers State University of New Jersey, Piscataway, NJ; Robert Wood Johnson University Hospital, New Brunswick, NJ; University of Medicine and Dentistry of New Jersey, New Brunswick, NJ.

PURPOSE: The interdisciplinary patient care model has been implemented in a number of clinical settings. Benefits of pharmacy services have been reported for numerous medical specialties. An effort was undertaken to 1) improve documentation of services provided by pharmacists to an ID consult service, and 2) characterize and summarize pharmacist-physician interactions on rounds.
METHODS: Pharmacists participated in daily ID rounds. Pharmacist services were documented in personal digital assistants (PDAs) using Pendragon Forms™ software. Data recorded included classification and detail of interaction, justification for proposed therapy changes, acceptance of recommendations by ID and primary medical groups, and patient outcomes. Data were uploaded into a personal computer and analyzed using Microsoft® Access.
RESULTS: From January through May 2001, 113 interactions were documented. The majority of interactions involved antimicrobial dose or frequency alteration (41%). Other common interactions included pharmacokinetic monitoring of vancomycin and aminoglycosides (18%) and reporting of adverse events (16%). Recommendations regarding antimicrobial selection (to narrow coverage or decrease costs) accounted for 10% of interactions. 108 (96%) recommendations were endorsed by ID physicians, of which 100 (93%) were implemented into patient care. Patient outcomes were categorized based on the types of recommendations made, with increased safety and decreased cost being the most common.
CONCLUSIONS: PDA software assists in the documentation and analysis of pharmacist services on ID rounds. The presence of pharmacists on ID patient rounds favorably impacts patient care through facilitating drug therapy decisions and supplementing the care provided by ID physicians.

185E. Cost impact of managing methicillin-resistant *Staphylococcus aureus* in a long-term care facility. Blair Capitano, Pharm.D., O. Alice Leshem, MS, RNC, Charles H. Nightingale, Ph.D., David P. Nicolau, Pharm.D., FCCP; Hartford Hospital; Hebrew Home and Hospital, Hartford, CT.

PURPOSE: The purpose of this study is to identify and quantify the resources consumed in the management of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) in a long-term care facility LTCF.
METHODS: This was a retrospective cohort study at a 375 bed LTCF. Institutional infection control records identified patients with infection due to either pathogen. A standardized data collection tool was utilized in conducting chart reviews. The medical and non-medical resources were identified, along with their costs.
RESULTS: An interim analysis was conducted on 21 MSSA and 28 MRSA infected patients. No difference in age, gender or type of infection was noted. The incidence of co-morbid conditions was similar; however, decubitus ulcers and diabetes were significantly higher in the MRSA group. MRSA infections were associated with significantly higher costs for general infection management, antibiotic, overall pharmaceutical, nursing and physician care. The overall infection related cost was significantly higher when due to MRSA ($3164.58 ± $2167.25) compared with MSSA ($1046.37 ± $877.54, p<0.001).
CONCLUSION: Infection with MRSA involves consumption of more healthcare resources and subsequently higher costs than infection due to MSSA in the LTCF setting. It appears that the major aspect of resource consumption is related to general care of the patient rather than the cost of pharmaceuticals. Treatment with antibiotics that allow for a faster cure rate may dramatically lower resource consumption and improve economic outcomes.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

186. Shifting from inpatient to outpatient treatment of deep vein thrombosis in a tertiary care center: a cost-minimization analysis. *Michel Boucher, B.Pharm., M.Sc.,* Marc Rodger, M.D., M.Sc., Mike Tierney, B.Sc., M.Sc., Jeffrey A. Johnson, Ph.D.; Canadian Coordinating Office for Health Technology Assessment, Ottawa, ON, Canada; Ottawa Hospital-General Campus, Ottawa, ON, Canada; Institute of Health Economics, Edmonton, AB, Canada.

PURPOSE: This study compared the cost of contemporary outpatient and historical inpatient management of proximal lower limb deep vein thrombosis (DVT) in adults.
METHODS: A cost-minimization analysis restricted to the hospital perspective was conducted. This design was justified based on the clinical equivalence of the two treatment strategies. All direct hospital costs for treating 51 consecutive patients with low molecular weight heparin in an ambulatory thrombosis clinic attached to a tertiary care hospital were measured. This data was compared to the cost of treating inpatient cases with unfractionated heparin obtained from a previous study conducted in the same patient population and institution in 1996. A subgroup of this study composed of 49 hospitalized patients who would have met criteria for outpatient treatment, should this option have been available then, was used as the control group. The analysis horizon was limited to 7 days, based on the duration of hospitalization and length of heparin therapy for DVT, before conversion to oral warfarin.
RESULTS: Data collection started in March 2000 and was completed in January 2001. The mean cost per outpatient case was C$ 257.24, which is

significantly different from the mean cost per inpatient case of C$ 2826.17 (adjusted for the difference in fiscal years; p<0.001). A breakdown of the outpatient cost showed that drugs contributed to 7.3% of this cost, medical imaging 15%, laboratory work 28.1% and, nursing time 49.6%.
CONCLUSION: Converting from inpatient to outpatient treatment of proximal DVT was associated with significant cost savings for the hospital.

187E. The impact of the community pharmacist in asthma. *William McLean, Pharm.D.,* Jane Gillis, Pharm.D., Ron Waller, M.Sc. (ClinPharm); Ottawa Hospital, Ottawa, ON, Canada; Lakeside Pharmacy, Kelowna, BC, Canada.

PURPOSE: Despite advances in recent years, asthma morbidity and mortality continue to increase. This study examined the failures and recommendations of past studies and introduced a new milieu for asthma care – the community pharmacy. The study incorporated a care protocol with the important ingredients of asthma education on medications, triggers and self-management, patient self-monitoring, pharmacists taking responsibility for outcomes, assessment of a patient's readiness to change and tailoring education to that, compliance monitoring, and physician consultation to achieve prescribing guidelines.
METHODS: 20 specially trained and certified pharmacists in British Columbia agreed to have patients or pharmacies randomized to enhanced (pharmaceutical) care (EC) or usual care (UC) for asthma patients. 642 patients were recruited of which 237 were analyzed for all 3 outcome categories. Patients were followed for one year.
RESULTS: Compared to usual care, patients in the enhanced care group had: symptom scores 50% decreased; peak flow readings 11 percent higher; days off work/school reduced about 0.6 days/ month; a reduction by 50% of the use of inhaled β-agonists; quality of life: an overall improvement of 19% and improvement in the specific domains of activity limitations, symptoms, emotional function; knowledge: a doubling of initial scores; ER visits: showed a 75% decrease in the EC group; medical visits: a 75% decrease. A patient satisfaction survey revealed a population extremely pleased by their pharmacy services. Economic analysis demonstrated a model which is more cost effective than usual care in terms of health care and some indirect costs in asthma.
CONCLUSION: Specially trained community pharmacists in Canada using a pharmaceutical care-based protocol can produce impressive improvements in clinical, economic and humanistic outcome measures in asthma patients. The health care system needs to produce incentives for such care.
Presented at the meeting of the Canadian Association for Population Therapeutics Meeting, Banff, AB, Canada, April 3, 2001.

188E. Costs of schizophrenia care associated with olanzapine, risperidone, or haloperidol in a public mental health system. Robert Damler, FSA, E. Anne Jackson, ASA, Teresa Wilder, ASA, *P. Joseph Gibson, Ph.D., MPH,* Janet L. Ramsey, M.S.; Milliman & Robertson Inc.; Eli Lilly and Company, Indianapolis, IN

OBJECTIVE: To assess the impact of schizophrenia medication choice on Medicaid costs.
METHODS: Michigan Medicaid claims from 1/1996 to 9/1997 were analyzed for persons with schizophrenia diagnoses initiating treatment with olanzapine (n=458), risperidone (n=481), or haloperidol (n=252). Changes in total adjusted Medicaid costs were compared between the
ttreatment groups one year before and after treatment initiation. Separate analyses were performed for dually Medicare and Medicaid enrolled patients (olanzapine n=801, risperidone n=606, haloperidol n=288).
RESULTS: Significant baseline differences existed between the groups. The olanzapine groups had more prior clozapine use, antipsychotic medications, and assertive community treatment than the risperidone and haloperidol groups, and fewer recent hospitalizations. For Medicaid non-dual enrollees, the average prior year costs were $13,120 per patient. After baseline adjustment, there were no significant differences in mean total cost change (olanzapine +$1112, risperidone +$1819, haloperidol +$1012). Excluding index medication costs, the olanzapine group's cost change (-$1106) was significantly lower than risperidone (+$529, p<0.0001) or haloperidol (+$717, p<0.0001). The average prior year costs were $8,492 per patient for Medicaid dual enrollees. When adjusting for baseline and excluding the index medication cost, results were similar to the results for Medicaid non-dual enrollees.
CONCLUSIONS: Decreases in service costs may indicate lower service use and greater patient benefit associated with olanzapine use, with no significant impact on total cost. These results will impact pharmacists' interpretation of Medicaid studies when evaluating the cost of various antipsychotics.
Presented at the Annual Meeting of the ENCP, Istanbul, Turkey.

189. Hospital charges in common percutaneous coronary intervention patients receiving abciximab vs eptifibatide. *Patrick L. McCollam, Pharm.D.,* Rebecca Luzadis, Ph.D.; Eli Lilly and Co, Indianapolis, IN; Miami University of Ohio, Oxford, OH.

PURPOSE: Patients with acute myocardial infarction (AMI), diabetes mellitus (DM) or unstable angina (UA) are commonly encountered in percutaneous coronary intervention (PCI). This study examined total hospital charges (TChg) in these patients in relation to treatment with abciximab versus eptifibatide.
METHODS: Data were from Solucient's Clinical Pathways Database (1/1/1999 to 12/31/1999). Inclusion criteria were: complete hospital billing data present, primary procedure code for PCI and treatment with abciximab or eptifibatide. Ordinary least squares regression was used to control for patient and hospital factors that may influence TChg.
RESULTS: Twelve hospitals met inclusion criteria. Unadjusted mean total charges were not significantly different between treatment groups. There were 1563 patients with AMI, 81.1% received abciximab. After controlling for differences in patient and hospital characteristics between treatment groups, incremental total hospital charges (includes drug charge) were not statistically significantly different between abciximab and eptifibatide recipients (p=0.09). There were 877 DM patients, 75.8% received abciximab. Similarly, total adjusted charges were not different between abciximab and eptifibatide recipients (p=0.25). Finally, there were 1670 UA patients, 72.6% received abciximab. Total adjusted charges were not different between treatments (p=0.26).
CONCLUSIONS: This study used "real world" data to examine TChg for commonly encountered PCI patients who received abciximab versus eptifibatide. After accounting for differences in patient and hospital characteristics, no significant difference in TChg, including drug charges, were observed in AMI, DM or UA patients treated with abciximab versus eptifibatide. These data again support examining the system perspective rather than drug acquisition cost alone.

190. Development of a systematic approach to evaluate medical resources associated with acute symptomatic thromboembolic events. *William J. Spruill, Pharm.D., FASHP*, William E. Wade, Pharm.D., FASHP, FCCP, Ryan B. Leslie, Pharm.D.; University of Georgia, Athens, GA.

PURPOSE: To develop a spreadsheet to: 1) identify all direct medical resources that may be utilized in patients with acute symptomatic venous thromboembolic events, and 2) quantify units of use of these resources, to assist with determination of institution specific direct medical costs of these events.
METHODS: Current Content and MEDLINE literature searches were conducted to identify all English language articles addressing direct medical resources commonly utilized in patients experiencing acute symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE). The resources were then assigned a priority level based on standards of practice, and quantified based on units of use typically required in the clinical arena.
RESULTS: Three major categories of resources were identified: diagnostic, treatment, and laboratory monitoring. Diagnostic procedures consisted of five sub-categories containing thirty-one cost resources; treatments consisted of nine sub-categories with twenty-six cost resources; while laboratory monitoring consisted of nine cost-resources. Units of use for diagnostic resources ranged from one to five; treatment units ranged from three to ninety-five; and laboratory monitoring resources from one to seventeen.
CONCLUSION: This spreadsheet allows any institution to accurately identify, prioritize, and analyze institution specific resource costs associated with the diagnosis, treatment, and laboratory monitoring of DVT and PE.

191. Early discharge of patients with community-acquired pneumonia using an aggressive home health care and once-daily outpatient parenteral antimicrobial therapy program. *Lawrence H. Dall, M.D.*; Midwest Hospital Specialists; University of Missouri at Kansas City, Kansas City, MO.

PURPOSE: The purpose of study was to document the feasibility of once-daily outpatient parenteral antimicrobial therapy (OPAT) and aggressive home health care of community-acquired pneumonia (CAP) patients to 1) treat patients in familiar environment, 2) reduce the risk of nosocomial infections, and 3) reduce the costs associated with treatment, with zero mortality.
METHODS: A 12-month, prospective multicenter study was conducted. Patients with Medicare + Choice who were CAP class II-IV (stratification for outcome as proposed by Fine, et al.) and considered to require hospitalization, were referred to the hospitalist group for treatment (N=92). Patients were treated in the hospital with intravenous ceftriaxone (CFTX) or, in penicillin-allergic patients, levofloxacin (LVFX) then released to home healthcare when clinically possible to complete the Home Pneumonia Program. Switch to oral azithromycin occurred when the patient could tolerate oral medications.
RESULTS: Use of the Fine et al. system to stratify patients was successful. Average length of hospital days was below one day and Home Pneumonia Program days was 3.4. There was zero mortality and a readmission rate of approximately 1%.
CONCLUSIONS: CAP is a leading cause of death in the US affecting 4 million adults annually. Inpatient care of CAP patients costs approximately $4 billion and generally occurs at a time of high hospital bed occupancy. Once-daily OPAT, accurate application of the Fine et al. stratification for patient selection, aggressive pulmonary toilet and aggressive nursing care resulted in the successful treatment of patients, reduced hospitalizations, and reduced cost with zero mortality and high patient satisfaction.

192. Evaluation of mandated cholesterol management: measuring clinical and economic outcomes. *E. Elledge, Pharm.D.*; Travis Air Force Base, CA.

In order to maintain or improve clinical outcomes, maximize cost-effectiveness, and standardize statin utilization, the Department of Defense (DoD) selected cerivastatin and simvastatin as the preferred HMG-CoA reductase inhibitors.
OBJECTIVE: To evaluate the clinical and economic outcomes of the therapeutic interchange within the DoD TRICARE Golden Gate region (Region 10).
METHODS: This multi-centered, longitudinal, retrospective database analysis compared pre- and post-conversion lipid parameters [LDL-C, total-C, HDL-C, and triglycerides (TG)] and pharmacy costs. Patients converted to cerivastatin or simvastatin from October 1999 to October 2000 were included if they had pre- and post-conversion lipid measurements, gender and date-of-birth. Paired t-tests were used to determine statistical significance.
RESULTS: Of the 742 patients meeting inclusion/exclusion criteria, 51.2% (380/742) were converted to cerivastatin and 48.8% (362/742) to simvastatin. Patients were converted from pravastatin (60.7%), atorvastatin (29.4%), fluvastatin (9.2%), or lovastatin (<1%).

Parameter (mean, mg/dl)	Pre-conversion	Post-conversion	p value
LDL-C	121.5	110.5	<0.001
Total-C	204.2	195.2	<0.001
HDL-C	46.9	49.1	<0.001
TG	178.4	178.1	0.76

Conversion resulted in annual pharmacy cost savings of $194.26/member.

CONCLUSION: The conversion to cerivastatin and simvastatin in a therapeutic interchange significantly improved LDL-C, total-C, and HDL-C in relation to pre-conversion values, with an annual pharmacy cost savings of $194.26/member. In light of the recently released NCEP ATP III guidelines, cost-effective treatment with statins will be even more important.

193. Cost-effectiveness analysis of cyclooxygenase-2-specific inhibitors (COX2I) compared with non-steroidal anti-inflammatory agents (NSAID) in Medicaid patients with mild rheumatoid- or osteoarthritis. *Daniel R. Touchette, Pharm.D., M.A.,* Michele Koder, Pharm.D., Kathy Ketchum, B.Pharm., MPA, HA, Dean Haxby, Pharm.D.; Oregon State University, Portland, OR.

PURPOSE: Clinical trials have demonstrated similar efficacy and lower gastrointestinal toxicity with COX2I compared with NSAID in mild arthritis. However, COX2I may be associated with higher cardiovascular risk in some patients and their acquisition cost is considerably higher than NSAID. We determined the cost-effectiveness of starting COX2I compared with NSAID for mild arthritic pain in patients not receiving aspirin.
METHODS: A Markov model was developed from an insurer's perspective (Medicaid) to predict the costs of care for patients taking a COX2I compared with an NSAID as the first-line agent. The Markov states included COX2I, NSAID, COX2I+ proton-pump inhibitor (PPI) for ulcer treatment and/or prophylaxis, NSAID + PPI, NSAID + misoprostol, and no therapy. Patients died from natural causes, gastrointestinal bleeding, or cardiovascular-related incidents. Possible adverse events (AE) included dyspepsia, gastrointestinal ulcer or hemorrhage, cardiovascular event, or "other" AE requiring change in therapy. Outcomes data was adapted from clinical literature, costs from reimbursements of a managed care Medicaid plan. One-way and other sensitivity analyses were conducted on all variables.
RESULTS: Starting therapy with an NSAID was the dominant strategy with a mean total cost of $8606 compared to $12,778 with COX2I (difference, $4172) and ten-year life expectancy of 9.1778 and 9.1597 life-years respectively (difference 0.0181). The model was sensitive to several variables, especially cardiovascular risk of COX2I.
CONCLUSION: Initial therapy with NSAID is more cost-effective for patients with mild arthritis, dominating COX2I in the base-case analysis. Further research is required to determine the true cardiovascular risk associated with COX2I.

194. Cost-effectiveness analysis of amifostine in patients with non-small cell lung cancer (NSCLC). *Daniel R. Touchette, Pharm.D., M.A.,* James G. Stevenson, Pharm.D., FASHP, Gail A. Jensen, Ph.D.; Oregon State University, Portland, OR; University of Michigan, Ann Arbor, MI; Wayne State University, Detroit, MI.

PURPOSE: While amifostine has been demonstrated to reduce the toxicity of some antineoplastic regimens, it is costly and its value in NSCLC is unknown. This analysis determined the cost-effectiveness of administering amifostine to patients with NSCLC from a hospital's perspective.
METHODS: A Markov model was developed to predict the costs of care for patients receiving cisplatin, carboplatin, or paclitaxel, with and without amifostine. Each monthly cycle, patients received chemotherapy or had it held. Outcomes and costs of toxicity (febrile neutropenia, thrombocytopenia, and anemia) were assigned to patients each month at a rate consistent with their treatment group. Inputs were derived from a clinical patient registry (patient identification), medication dispensing (transition rates) and laboratory databases (blood product administration), clinical literature (effect of amifostine), and costing catalogs (cost of blood products, medications, and their administration). One-way sensitivity analyses and Monte Carlo analysis were conducted.
RESULTS: Fifty-eight patients with NSCLC made 199 visits for chemotherapy during the study period. Paclitaxel was administered 39% of the time, carboplatin 38%, and cisplatin 23%. Eight units of packed red blood cells were required and four patients were admitted for febrile neutropenia. Average cost for amifostine $4421 compared with $2709 for controls (difference $1711). For every 100 patients treated, 8 adverse events were avoided with an incremental cost-effectiveness ratio of $21,388 per AE avoided.
CONCLUSION: Amifostine results in higher treatment costs to the hospital when used for preventing toxicity from common NSCLC antineoplastic regimens. Further analysis is warranted including outcomes and costs of non-hematologic toxicities and radiation therapy.

195. Retrospective evaluation of unanticipated admissions and readmissions after same day surgery and associated costs. *Kim C. Coley, Pharm.D.,* Brian A. Williams, M.D., M.B.A., Stacey V. DaPos, M.S., Connie Chen, Pharm.D., Randall B. Smith, Ph.D.; University of Pittsburgh, Pittsburgh, PA; Pharmacia Corporation, Peapack, NJ.

PURPOSE: Unanticipated admissions and readmissions following same day surgery (SDS) are important quality markers that have significant cost implications. With the growing number and complexity of outpatient procedures, it is important to characterize post-surgical outcomes. The objectives of this study were to determine the rate of unanticipated admissions and readmissions and to identify the associated reasons and costs.
METHODS: We retrospectively identified all SDS procedures performed during 1999 at a university teaching hospital through a computerized search of a medical records database. Outcomes included 30-day return rates, reasons for return, and costs.
RESULTS: A total of 20,817 patients underwent SDS in 1999. Unanticipated admission or readmission directly related to the original SDS procedure occurred in 341 (1.6%) patients. Pain was the most commonly reported reason for return, occurring in 124 (36%) patients with unanticipated admission or readmission. The general surgery service had the highest rate of unanticipated admissions or readmissions (3.4%), followed by otolaryngology and urology (both 3.1%). Of the 124 patients returning with unanticipated admissions and readmissions due to pain, 46 (37%) of these had SDS orthopedic procedures. Mean (SD) charges for patients with pain were $1952 ($4653) per visit, whereas non-pain related charges were $16,134 ($51,845).
CONCLUSION: At our teaching institution, approximately 1.6% of patients undergoing SDS return due to problems directly related to the original procedure. Pain accounted for more than one-third of returns, incurring significant costs. Pain management strategies should be improved and evaluated to determine if they can lead to favorable clinical and economic outcomes.

196E. Five year follow-up of a program to minimize inappropriate use of parenteral nutrition. *Rex A. Speerhas, R.Ph., BCNSP,* Douglas L. Seidner, M.D., Ezra Steiger, M.D.; Cleveland Clinic Foundation, Cleveland, OH.

PURPOSE: A mandatory program to limit inappropriate parenteral nutrition (PN) use was started in April 1994 when a drug use evaluation (DUE) showed only 59% of patients given PN met basic criteria for therapy. Follow-up DUEs were performed to see if inappropriate use of PN decreased and if patient care had been adversely affected.
METHODS: The DUE was repeated 5 months after program implementation and again 5 years later. Hospital systems were queried for admissions, illness severity, length of stay (LOS), 30-day mortality, and PN pharmacy cost. T-test analysis compared each year after program implementation with the year prior to implementation. The program consists of a mandatory consultation to the nutrition support team (NST) prior to starting PN in all adult patients. Patients are either approved for PN or advised to use enteral nutrition. The number of daily PN bags dispensed by pharmacy from 1993-1999 was collected and adjusted for patient days in the hospital and ICU and was compared to LOS and mortality. Appropriate PN use meant a non-functioning gastrointestinal tract and use of therapy for ≥ 5 days.
RESULTS: Repeat DUEs showed PN was appropriate 70% and 83% of the time, respectively. T-test analysis for PN dispensed 1994-1999 shows there is significant reduction (p=0.001) compared to 1993. LOS and mortality were unchanged. Yearly cost savings due to decreased use of PN compared to 1993 averaged 38%.
CONCLUSION: NST involvement has significantly decreased inappropriate use of PN and resulted in sustained cost savings without adversely affecting patient outcomes.
Presented at the 26th Annual Clinical Congress of the American Society for Parenteral and Enteral Nutrition, Chicago, IL, January 21-24, 2001.

197E. Cost of opioid-related adverse drug events in surgical patients. *Gary M. Oderda, Pharm.D., MPH,* Matthew Samore, M.D., John Burke, M.D., Arthur Lipman, Pharm.D., Michael Ashburn, M.D., M.P.H., R. Scott Evans, Ph.D., James Lloyd, Connie Chen, Pharm.D.; University of Utah, Salt Lake City, UT; LDS Hospital, Salt Lake City, UT; Intermountain Health Care, Salt Lake City,

UT; Pharmacia Corp., Chicago, IL.

RATIONALE: Opioids have demonstrated efficacy in the treatment of post-operative pain, however, their use is oftentimes limited by adverse events.
PURPOSE: To determine the adverse drug event (ADE) rate, attributable excess length of stay (LOS), costs, and mortality in adult surgical patients who received opioids.
METHODS: A hospital based computer system detects potential ADEs which are verified by pharmacists using a consistent protocol and stored in an ADE database. Patients were selected from this database if they were 18+ years and received an opioid during a surgical hospitalization between 1/1/90 and 12/31/99. Control patients were matched for each case by LOS at least as long as time to ADE, age ± 10, gender, admission year and major disease category. A paired t-test and linear regression models were used to examine differences in attributable LOS and costs in the cases and matched controls and determine the predictors of increased LOS, total hospital costs.
RESULTS: 60,722 patients received opioid medication during their surgical hospitalization and 2.7% experienced an opioid related ADE. The most common clinical manifestation was nausea/vomiting. No mortality difference was seen (p=0.147). A paired t-test, comparing attributable differences cases and controls showed a statistically significant increase in LOS (0.66 days; 95% CI 0.36, 0.97; p<0.001) and cost ($714; 95% CI $87, $1359; p=0.026) in patients experiencing an opioid related ADE. Linear regression showed an increase in LOS (0.72, p<0.000001) and cost ($584.4, p=0.045).
CONCLUSIONS: Opioid related ADEs are common in hospitalized patients and increase LOS and hospital costs.
Presented at the 2001 Annual Meeting of the American Society of Anesthesiologists, New Orleans, LA, October 13-17, 2001.

Pharmacoepidemiology

198. The completeness of published case reports of significant adverse drug events. *William N. Kelly, Pharm.D.*; Mercer University, Atlanta, GA.

PURPOSE: To discover the completeness of published case reports on significant adverse drug events (ADEs).
METHODS: Case reports of ADEs published in *Clin-Alert* between the mid-1970s and the mid-1990s were the source of significant ADEs. A significant ADE is one that involves an outcome of death, permanent disability, or life-threat. The significant ADE reports were reviewed for the presence of sixteen patient, seven drug, and six event variables. If the report was about a drug interaction, medication error, or medication allergy, nine other variables were checked. Cases were stratified by type of outcome.
RESULTS: Nine percent (1520) of *Clin-Alert* reports concerned significant ADEs. The reports were 97% accurate and 98% complete when compared with the full, published journal reports. The completeness of reports did not vary by type of outcome. Three patient variables were reported more than 90% of the time, while the other thirteen patient variables were reported less than 25% of the time. Only one of drug variable was reported more than 90% of the time, while the other six drug variables were reported 14%-74% of the time. Most of the event variables were reported most of the time. Added information for drug interactions, medication errors, and medication allergies were reported 61%-99% of the time.
CONCLUSION: A large sample of case reports of significant ADEs published over a twenty-year period, as reported by *Clin-Alert*, lacked important information that would help other practitioners, and drug safety researchers. Guidelines are needed on how to prepare significant ADE reports for publication.

199. Drug therapy and risk factors related to hospitalization and mortality outcomes among patients with congestive heart failure in Ohio Medicaid. *Robert J. Cluxton, Pharm.D.,* Janet M. Riga, Pharm.D., Jeff J. Guo, Ph.D., Pamela C. Heaton, M.S., Michael M. Bottorff, Pharm.D.; University of Cincinnati, Cincinnati, OH.

OBJECTIVE: To evaluate the associations of congestive heart failure (CHF) treatment guidelines and outcomes of hospitalization, emergency room visits and mortality in Ohio Medicaid patients.
METHODS: Data source was Ohio Medicaid claims database from 7/1/1997 to 12/31/1999. Subjects were newly diagnosed as indicated by ICD9 428.0. Use of ACE-inhibitors and β-blockers was categorized into a categorical variable, AceiBB. Two logistic regression models were conducted. Model #l: ER-hospitalization/days-of-study-length = AceiBB, sex, age, race, digoxin, diuretics, spironolactone, hydralazine and isosorbide. Model #2: Mortality = AceiBB, sex, age, race, digoxin, diuretics, spironolactone, hydralazine and isosorbide.
RESULTS: Of 3945 patients, 552 (13.9%) were hospitalized and 56 (1.4%) patients died during the 12-month study period. A total of 1261 (32%) patients received an ACE-inhibitor or β-blocker, while 1489 (37.7%) patients received only diuretics or digoxin. Odds ratio for hospitalization with AceiBB was OR 0.87 (95% CI 0.61, 1.22), white patients OR 1.26 (95% CI 1.03, 1.53), isosorbide OR 1.34 (95% CI 1.06, 1.66), digoxin therapy OR 1.48 (95% CI 1.30, 1.67), spironolactone OR 1.90 (95% CI 1.46, 2.39), diuretics OR 2.29 (95% CI 1.87, 2.82), and hydralazine OR 2.33 (95% CI 1.31, 3.78). Increased mortality was significantly associated only with advanced age OR 1.04 (95% CI 1.02, 1.06).
CONCLUSIONS: No significant association was found for use of ACE-inhibitor or β-blocker for either odds of hospitalization or mortality. Patients with treatment of digoxin, diuretics, spironolactone, hydralazine or isosorbide had higher rate of hospitalization, but did not show with higher risk of mortality. These associations may reflect more treatment of advanced disease, inappropriate drug use, or insufficient study period to develop the outcomes of interest.

200. Mortality rates from adverse drug reactions in the United States 1981 to 1998. *Lisa C. Hutchison, Pharm.D.*; University of Arkansas for Medical Sciences, Little Rock, AR.

PURPOSE: Mortality data from the National Center for Injury Prevention and Control was evaluated to describe the epidemiology of adverse drug reactions (ADRs).
METHODS: The database of death certificate information was queried for mechanism or cause of injury ascribed to International Classification of Diseases (ICD) codes E930-E949 Drugs, medicinal and biological substances causing adverse effects in therapeutic use, as listed on death certificates. These ICD codes exclude accidental overdoses, medication errors, drugs administered with suicidal or homicidal intent. They include adverse effects due to allergy or hypersensitivity reactions. The years of 1981 to 1998 (all that are available in the database) provide an epidemiological description of ADRs among various groups, by gender, age, race and geographic region.
RESULTS: The age-adjusted rate began at 0.08 per 100,000 in 1981, fell to 0.04 per 100,000 in 1989 and rose to 0.08 per 100,000 in 1998. The West had the lowest mortality rate for every year. Deaths due to ADRs show an association with age, rising from 0.01 to 0.38 per 100,000. Similar rates are seen between men and women. Rates are higher in blacks than whites.
SUMMARY: There is an increase in mortality due to ADRs in recent years in the United States. Geographic and racial differences are seen, but no difference is seen between genders.

Pharmacogenomics

201. Caspofungin inhibition of histamine-n-methyltransferase identified by differential gene expression. *John D. Cleary, Pharm.D.,* P. David Rogers, Pharm.D., Stanley W. Chapman, M.D.; University of Mississippi, Jackson, MS.

BACKGROUND: Toxicity and activity of caspofungin (MK0991, Cancidas) may be predictable based on changes in gene expression profiles. We evaluated the affects of Caspofungin on human monocytic cells (THP-1) gene expression *in vitro* to identify mechanisms of toxicity.
METHODS: THP-1 cells (3.0×10^7 cells were exposed for 6 hours to caspofungin or media. Total RNA was isolated from cells using the TRIazole reagent. cDNA was synthesized using anchoring primers then amplified in the presence of P^{33}dCTP. Complimentary DNA were then hybridized to a human gene array containing >4300 known genes. The identity of specific genes with altered regulation (>2 fold) was performed by using variable intensity analysis between the two exposures. Significant genes are validated using RT-PCR with unique primers.
RESULTS: Twenty-four up and 89 down-regulated cDNAs were considered unique to anti-fungal exposure. For common gene categories; DNA associated protein, cellular receptors and enzymes, and altered transcription were similar. However, decreases in genes associated with histamine toxicity were significant. The transcript for histamine-N-methyltransferase was down-regulated. This enzyme inactivates histamine by N-methylation. Decreased amounts of this enzyme could explain the histamine reactions (rash, facial swelling, pruritis and warmth) associated with this agent's administration. Several yeast homologs were also identified and could be a source of novel mechanisms of antifungal efficacy.
CONCLUSIONS: These studies have identified a number of monocytic mRNA representing altered gene regulation associated with caspofungin. Further investigation may still elucidate novel pathways involved in human toxicity and activity against yeast.

202. Genetic polymorphism in the 5'-flanking region of CYP1A2 gene in Caucasians. *Yuen Yi Hon, Pharm.D.,* Scott R. Penzak, Pharm.D., Kara L. Shirley, Pharm.D., Michael W. Jann, Pharm.D.; Mercer University, Atlanta, GA.

PURPOSE: This study determined the allele frequencies for a genetic polymorphism at nucleotide -2964 (guanine to adenine) in the 5'-flanking region of the CYP1A2 gene in a small group of healthy unrelated Caucasians. Subjects were phenotyped for CYP1A2 activity with caffeine. Frequency of the mutant allele was compared with previously published data in a Japanese population.
METHODS: Genotype of subjects was determined using a baseline blood sample by polymerase chain reaction – restriction fragment length polymorphism analysis. Chi-square test was used to compare the frequency of the mutant allele in this population with previous published data. CYP1A2

phenotype was determined by caffeine metabolism. After 200-mg caffeine administration, blood (4 h), saliva (6 h and 10 h), and urine (8 hours total) were collected for HPLC analysis of caffeine and its metabolites.
RESULTS: No mutations at nucleotide –2964 were found in 12 Caucasians (11 males, 1 female). Whereas the estimated allele frequencies in this study were 1.0 and 0 for the wild type and mutant allele respectively, frequencies for these alleles were 0.77 (wild type) and 0.23 (mutant) in a previously described Japanese study (n=116). There was a significant difference (χ^2 6.91, $p<0.01$) in the frequency of the mutant allele between this Caucasian population and the Japanese population. Allele frequencies in Caucasians need to be confirmed in a larger population study. Pending results of phenotype analysis will be presented at the meeting.
CONCLUSIONS: Guanine to adenine polymorphism at nucleotide –2964 in the 5'-flanking region of the CYP1A2 gene appears to be less common in Caucasians than in Japanese.

203. Ethnic differences in the distribution of P-glycoprotein polymorphism among Caucasians and African-Americans. Vicki L. Ellingrod, Pharm.D., BCPP, *David I. Min, Pharm.D., FCCP,* Craig Herman, Pharm.D. candidate; University of Iowa, Iowa City, IA.

Recently alterations in the human multi-drug resistance (MDR-1) gene have been found to correlate with the C3435T polymorphism of P-glycoprotein (P-gp). Individuals homozygous for this polymorph have significantly lower MDR-1 expression and higher plasma concentrations of P-gp substrates such as digoxin. Ethnic differences in the pharmacokinetics of some P-gp substrates have been found.
PURPOSE: To determine if there are differences in the distribution of P-gp polymorphism between Caucasian and African American subjects.
METHODS: DNA was isolated from African American and Caucasian subjects using a salt precipitation method. The samples were genotyped for the C3435T polymorphism of PGP using the polymerase chain reaction and a restriction digest (Hoffmeyer, et al 2000). Allele frequencies of the C and T polymorphism were compared between groups using a fisher's exact test.
RESULTS: A total of 97 Caucasians and 15 African Americans were included in this study. The frequency of the C allele was 82% in the Caucasian sample and 48% in the African American sample, while the frequency of the T allele was 18% and 52% in the two respective samples. The distribution of alleles was statistically different between the two groups (p=0.0009).
CONCLUSION: Differences in the expression of P-gp polymorphism exist between Caucasian and African American populations. This may partly explain the basis for ethnic pharmacokinetic differences often seen with P-gp substrates. Continued work in this area needs to be done to relate these differences in the polymorphic expression of P-gp and the pharmacokinetic parameters of various P-gp substrates.

204. Pharmacokinetic and pharmacodynamic consequences of CYP2C9 genetic polymorphisms with losartan. *Craig R. Lee, Pharm.D.,* John A. Pieper, Pharm.D., FCCP, BCPS, Joyce A. Goldstein, Ph.D., Joyce Blaisdell, B.S., Morris J. Clarke, Ph.D., Alan L. Hinderliter, M.D.; University of North Carolina at Chapel Hill, Chapel Hill, NC; National Institute of Environmental Health Sciences, Research Triangle Park, NC.

PURPOSE: The pharmacokinetics and pharmacodynamics of losartan were evaluated in subjects of known *CYP*2C9 genotype, the isozyme responsible for conversion of losartan to its pharmacologically active metabolite (E3174).
METHODS: Fifteen healthy volunteers expressing the *CYP*2C9*1*1 (wild-type), *1*2 or *1*3 genotype received a single 50-mg oral dose of losartan, with serial plasma sampling and supine blood pressure (BP) determinations over 24 and 12 hours, respectively. Losartan and E3174 plasma concentrations were determined by a validated HPLC assay. The area under the concentration-time curve ($AUC_{0-\infty}$) for both losartan (LOS $AUC_{0-\infty}$) and E3174 (E3174 $AUC_{0-\infty}$) was determined by noncompartmental analysis. The area under the effect-time curve ($AUEC_{0-12}$) was calculated by evaluating the absolute reductions in both systolic (SBP $AUEC_{0-12}$) and diastolic BP (DBP $AUEC_{0-12}$) from baseline over time. Statistical analysis across the genotyped groups was performed by analysis of variance.
RESULTS: Results are presented as means (SD).

	*1*1	*1*2	*1*3	p-value
N	5	5	5	
LOS $AUC_{0-\infty}$ (ng•hr/ml)	444.2 (140.9)	736.5 (292.3)	536.7 (122.5)	0.10
E3174 $AUC_{0-\infty}$ (ng•hr/ml)	1873.3 (322.4)	1811.3 (341.9)	2155.8 (865.9)	0.61
SBP $AUEC_{0-12}$ (mm Hg•hr)	70.4 (89.6)	68.7 (62.2)	71.1 (34.2)	0.99
DBP $AUEC_{0-12}$ (mm Hg•hr)	94.9 (155.7)	92.8 (64.0)	58.7 (53.3)	0.85

CONCLUSIONS: *CYP*2C9*1 heterozygotes did not demonstrate significant changes in losartan or E3174 pharmacokinetics, or systolic and diastolic BP compared to wild-type volunteers after single dose losartan administration. The effects of *CYP*2C9 genotype on losartan pharmacokinetics and pharmacodynamics in patients with cardiovascular disease and other *CYP*2C9 substrates remain to be determined.

205E. Erythromycin breath test (ERMBT): a basis for sex differences, and lack of effect of CYP3A expression and MDR1 genotypes. *Y. Sunila Reddy, Pharm.D.,* Paul B. Watkins, M.D., Mary F. Paine, Ph.D., Erin G. Scheutz, Ph.D., Jatinder Lamba, Ph.D., Seboo Dhakhwa, B.S., Angela D.M. Kashuba, Pharm.D.; University of North Carolina at Chapel Hill, Chapel Hill, NC; St. Jude Children's Research Hospital, Memphis, TN.

PURPOSE: ERMBT result is believed to quantify liver CYP3A4 activity. However, ERM is a substrate for PGP (MDR1 gene product), and may be metabolized by CYP3A5. Also, ERMBT assumes a CO_2 production of 5 mmol/min/m^2. We investigated the influence of *MDR1, CYP3A5*, and measured CO_2 on ERMBT.
METHODS: After direct measurement of CO_2 production rate, ERMBT and IV midazolam (MDZ; 0.025 mg/kg) was administered to 30 (15M; 15F) healthy volunteers. ERMBT at 60 min ($^{14}CO_{2\ 60\ min}$) and the reciprocal of time to peak breath $^{14}CO_2$ ($1/T_{max}$) were determined. Plasma was collected over 6 hours and analyzed for MDZ (LC/UV) and total radioactivity (R; liquid scintillation). PGP (exon 21 and 26) and CYP3A (CYP3A4 NFSE and CYP3A5) genotype was obtained by PCR.
RESULTS: Mean $^{14}CO2_{\ 60min}$ in women was significantly greater than in men using estimated CO_2 ($p=0.01$) as previously reported. However, the sex difference was not significant using measured CO_2 ($p=0.1$). Using ANOVA analyses, neither heterozygous nor homozygous *MDR1* genotypes associated with decreased PGP function had detectable effects on $^{14}CO_{2\ 60\ min}$ ($p>0.58$) , $1/T_{max}$ ($p>0.17$) or clearance of R ($p>0.88$). Individuals expressing CYP3A5 (n=6) did not have altered ERMBT ($p>0.2$) or clearance of MDZ ($p>0.4$) relative to CYP3A5 nonexpressors (n=19). CYP3A4 NFSE polymorphism also did not affect ERMBT or MDZ measures ($p>0.5$).
CONCLUSIONS: Prior reports of sex differences in ERMBT results may largely reflect differences in CO_2 production and not CYP3A4 activity. This study does not support ERMBT or MDZ being influenced by PGP or CYP3A genetic polymorphisms.
Presented at the 6th International Meeting of the International Society for the Study of Xenobiotics, Munich, Germany, October 7-11, 2001.

Pharmacokinetics/Pharmacodynamics/ Pharmacometrics/Drug Metabolism

206. Levofloxacin pharmacokinetics in patients with end-stage renal disease. Aroonut Lucksiri, Pharm.D., M.S., Michael B. Kays, Pharm.D., Richard J. Hamburger, M.D., Bruce A. Mueller, Pharm.D., Meri K. Scott, Ph.D., *Kevin M. Sowinski, Pharm.D.*; Purdue University, Indianapolis, IN.

PURPOSE: No published data are available describing the pharmacokinetics of levofloxacin in patients with end-stage renal disease (ESRD). The objectives of this study were to determine the impact of ESRD on levofloxacin pharmacokinetics and to evaluate the peak concentration to MIC ratio against common respiratory pathogens.
METHODS: Eight subjects with ESRD, with no measurable residual renal function, received 250 mg levofloxacin as an intravenous infusion over one hour immediately following a regularly scheduled dialysis session. Blood samples for the determination of levofloxacin concentrations were obtained immediately before and at 0.5, 1, 1.5, 2, 3, 5, 24, and 44 hours after the infusion started. Levofloxacin concentrations were determined by a validated HPLC method. Differential equations describing a two-compartment open infusion pharmacokinetic model were fitted to each individual subject's levofloxacin serum concentration-time data by iterative nonlinear weighted least squares regression analysis using ADAPT II computer software. Median peak concentration to MIC90 ratios were calculated for *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Klebsiella pneumoniae* using MIC data from published studies.
RESULTS: Subjects (2F/6M) were 53 ± 12 years old and weighed 70 ± 16 kg. Individual and median pharmacokinetic estimates were:

Subject	Systemic Cl (mL/min)	Distribution (mL/min)	Vc (L)	Vp (L)	Vss (L)	$t_{1/2}$ (hours)	Cmax (µg/L)
1	40.6	1060	12.3	89.1	101.4	29.7	5.26
2	34.1	680	28.0	108.3	136.3	47.6	4.95
3	12.7	382	11.0	29.7	40.6	37.5	11.36
4	41.3	1420	23.0	80.4	103.4	29.5	4.05
5	35.9	484	15.8	54.3	70.0	23.6	7.87
6	29.9	859	22.6	93.2	115.7	45.7	4.99
7	25.9	879	14.9	63.0	77.9	35.5	5.45
8	41.9	930	29.7	110.2	139.9	39.7	4.18
Median	35.0	868	19.2	84.7	102.4	38.5	5.13

Vc, Vp and Vss = volume of distribution in the central and peripheral compartments and at steady-state, respectively

At this dose, the median peak/MIC90 ratio was ≥ 10 for *H. influenzae*, *M. catarrhalis*, *E. cloacae*, and *K. pneumoniae*, 5 for *S. pneumoniae*, and <0.5 for *P. aeruginosa*.
CONCLUSIONS: The pharmacokinetics of levofloxacin in patients with

ESRD treated with hemodialysis are similar to patients with renal insufficiency (Clcr <20 ml/min). In these patients, levofloxacin 250 mg IV provides peak/MIC90 ratios >10 for common respiratory pathogens, with the exception of *S. pneumoniae* and *P. aeruginosa*.

207. Age-related changes in blood-brain barrier p-glycoprotein function. *Kathryn K. Neill, Pharm.D.,* Mark S. Luer, Pharm.D., Melissa L. Shannon, Bill J. Gurley, Ph.D.; University of Arkansas for Medical Sciences, Little Rock, AR.

PURPOSE: To determine if aging affects blood-brain barrier (BBB) p-glycoprotein function.
METHODS: Using a crossover design, age-controlled male SD rats (3 or 23 months) were administered saline or cyclosporine (CSA; p-glycoprotein inhibitor). Quinidine (p-glycoprotein substrate) 12.5 mg/kg IV was administered 2 h later. Intracerebral microdialysis (brain extracellular fluid; ECF) and blood (serum) were collected. Quinidine in ECF and serum was quantified by HPLC. Pharmacokinetic parameters were calculated (non-compartmental analysis) and compared between age groups and treatment arms (ANOVA).
RESULTS: Six rats (3/age group) were evaluated. Quinidine pharmacokinetic parameters (mean ± SD) were: AUC_{ECF} 452 ± 267, 489 ± 402, 1339 ± 173, 751 ± 253 ng·h/ml; AUC_{RATIO} ($AUC_{ECF}/AUC_{unbound\ serum}$) 0.57 ± 0.11, 0.51 ± 0.12, 1.76 ± 0.48, 1.05 ± 0.13; and ECF-t1/2 1.27 ± 0.17, 2.30 ± 0.91, 1.45 ± 0.02, 4.74 ± 2.20 hr for young-saline, old-saline, young-CSA, and old-CSA treated rats, respectively. No serum parameters (AUC_{total}, $AUC_{unbound\ serum}$, CL, V_{ss}, t1/2, MRT, and f_u) were significantly altered by age and/or treatment. CSA significantly ($p<0.05$) increased AUC_{ECF} and AUC_{RATIO} independent of age and increased ECF-t1/2 only in aged rats; while aging significantly increased ECF-t1/2 independent of treatment and increased AUC_{RATIO} only in CSA-treated rats.
CONCLUSIONS: CSA elevated quinidine brain concentrations relative to serum consistent with enhanced brain uptake and/or BBB p-glycoprotein inhibition and aging increased quinidine's brain elimination half-life consistent with diminished central compartment efflux. Each factor influences the CNS disposition of the p-glycoprotein substrate, quinidine, however the mechanism(s) have yet to be elucidated.

208. Predictive approaches to overall survival following high-dose chemotherapy for advanced breast cancer utilizing cyclophosphamide pharmacokinetics and pharmacogenetics. *William Petros, Pharm.D., FCCP,* Penelope Hopkins, Ph.D., James Vredenburgh, M.D., Susan Spruill, M.S., Gloria Broadwater, M.S., Jeffrey Marks, Ph.D., Jeff Hall, Ph.D., Michael Colvin, M.D.; Duke University Medical Center, Durham, NC; PPGx, La Jolla, CA.

PURPOSE: This study evaluated the relationship between cyclophosphamide (CY) systemic exposure (AUC) and overall survival in patients receiving high-dose CY-containing chemotherapy. In addition, we compare these data to that which we previously reported for a genotype association study in these same patients.
METHODS: The study population was 86 chemotherapy naive female patients with metastatic or inflammatory breast cancer who participated in a trial of high-dose CY, cisplatin and BCNU chemotherapy. Parent plasma CY disposition was evaluated by HPLC in 36 timed concentrations/patient collected over the three days of CY administration (1875 mg/m2/day). A standard two-stage approach to pharmacokinetic parameter estimation was utilized. Peripheral blood lymphocytes were genotyped for single nucleotide polymorphisms (SNPs) suspected to be involved in CY metabolism by PCR.
RESULTS: Patients were followed for a median of 8.2 years prior to this analysis. Patients with parent CY AUC above the median value (implying a slower conversion to the active metabolite) had a shorter survival than those with AUC below the median (1.8 vs 3.8 years, respectively; p=0.042). These results are in concordance with our previous report that a SNP in the CYP450 3A4 promoter correlated to worse overall survival and reduced CY metabolism (1.3 vs 2.7 years, p=0.043; Proc Am Assoc Cancer Res 2001;42:1435). The Spearman correlation coefficient between CY AUC and the CYP450 3A4 SNP was 0.23 (p=0.08).
CONCLUSIONS: Inter-patient variability in CY AUC may be the cause of some breast cancer-related deaths following high dose chemotherapy. Both genotyping and CY pharmacokinetic monitoring appear to be reasonable strategies for prospective dose individualization trials.

210E. In vivo disposition of ^{14}C ertapenem in healthy male and female volunteers. Brad Wond, Donald G. Musson, Kimberly L. Birk, Liwen Xi, Sherry Holland, Goutam Mistry, Paul Deutch, John D. Rogers, *Anup K. Majumdar,* Scott Waldman; Merck Research Laboratories, West Point, PA; Thomas Jefferson University Hospital, Philadelphia, PA.

BACKGROUND: Ertapenem (INVANZ®) is a new long-acting once-a-day parenteral broad-spectrum antibiotic for a variety of infections. The metabolism, elimination and recovery of ertapenem following a 1-g IV dose of ^{14}C-ertapenem (~104 uCi) are presented.
METHODS: A single-dose study was conducted in 7 healthy subjects by administering a 1-g IV dose of ^{14}C-ertapenem (~104 uCi) over 30 minutes. Plasma samples were collected over 48 hours, and urine and feces over 168 hours. Plasma and urine samples were analyzed for unchanged ertapenem using a reverse-phase HPLC method with UV detection. Plasma, urine, and feces samples were also analyzed for total radioactivity using liquid scintillation spectrometry. Metabolite profiles were determined in urine using gradient elution liquid chromatography with radiometric detection.
RESULTS: The radioactivity in plasma was accounted for primarily by unchanged ertapenem. The mean AUC ratio of unchanged ertapenem/radioactivity was 0.94. Mean recovery of total radioactivity was ~80% and ~10% of the dose in urine and feces, respectively. The major metabolite of ertapenem in human urine was the ring-opened derivative formed by hydrolysis of the β-lactam ring. Together ertapenem and the ring-opened metabolite accounted for 95% of the radioactivity in urine. Each accounted for about an equal fraction of urinary radioactivity.
CONCLUSIONS: Plasma radioactivity consists predominantly of ertapenem after IV infusion of radiolabeled ertapenem. The majority (80%) of the dose is excreted in urine and only a small percent (~10%) is eliminated by biliary/fecal excretion. About equal amounts of ertapenem and its β-lactam ring-opened metabolite account for 95% of radioactivity excreted in urine.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

211E. Pharmacokinetics of ertapenem in healthy young volunteers. *Anup K. Majumdar,* Donald G. Musson, Kimberly L. Birk, Chester J. Kitchen, Sherry Holland, Jackie McCrea, Goutam Mistry, Michael Hesney, Liwen Xi, Susan S. Li, Rita Haesen, Paul Deutsch, John D. Rogers, Robert Blum, Robert Lins, Scott Waldman; Merck Research Laboratories, West Point, PA; Millard Fillmore Hospital, Buffalo, NY; A.Z. Stuivenberg, Antwerpen, Belgium; Thomas Jefferson University Hospital, Philadelphia, PA.

BACKGROUND: Ertapenem (INVANZ®) is a new long-acting once-a-day parenteral broad-spectrum antibiotic for a variety of infections. The PK of IV ertapenem in healthy young volunteers are presented.
METHODS: Single- and multiple-dose PK of ertapenem at doses up to 3 g were obtained in healthy young subjects. Plasma and urine samples collected were analyzed using reverse phase HPLC with UV detection.
RESULTS: The single dose $AUC_{0-\infty}$ of ertapenem was nearly dose-proportional over the dose range of 0.5 to 2 g. At the therapeutic dose of 1 g IV (30 min infusion), the mean plasma clearance (Cl_P) across studies ranged from ~27 to 30 ml/min; the mean plasma concentration at the end of infusion ranged from ~145 to 175 µg/ml, at 6 hr from ~30 to 340 µg/ml, and at 12 hour from ~9 to 11 µg/ml. The mean plasma t1/2 ranged from 3.8 to 4.4 hours. About 40 to 50% of Cl_P was via renal clearance (Cl_R). The $AUC_{0-\infty}$ of ertapenem was similar in males and females following the 1-g dose. Concentrations after single and multiple doses were similar.
CONCLUSIONS: The pharmacokinetics of ertapenem are nearly dose-proportional up to a 2 g IV dose. Mean plasma concentrations of total ertapenem at 12 hour following the 1-g dose are well in excess of the proposed susceptibility breakpoint for ertapenem of 4 µg/ml. There is no clinically significant difference in the PK of ertapenem in males and females. Ertapenem does not accumulate after multiple dosing.
Presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

212. Rational empiric dosing strategy of cefepime against *Pseudomonas aeruginosa* (PA): integrating population pharmacokinetics (PPK), pharmacodynamics (PD) and microbiologic surveillance. *Vincent H. Tam, Pharm.D.,* Arnold Louie, M.D., George L. Drusano, M.D.; Albany Medical College, Albany, NY.

PURPOSE: Substantial resources are devoted to describe drug behavior in humans, the relationship between drug exposure and outcomes, and geographic susceptibilities of pathogens to antimicrobials. However, a concerted effort to translate such data to clinically useful information to improve outcome is relatively lacking. We illustrate such an approach using cefepime against PA, which therapy is often empiric in critical care settings.
METHODS: Adopting a published cefepime PPK 2 compartment model, we used Monte-Carlo simulation to derive the steady state PK profiles of 1000 patients each with creatinine clearance of 120, 90 and 60 ml/min. Based on recent MIC distribution of PA against cefepime in the U.S., a weighted approach was employed to assess the likelihood that standard (2g q12h) and maximal (2 g q8h) dosing recommendations would achieve PD target of 80% probability of microbiologic success. Similar assessments were also made with standard dosing, with each dose infused over 6 hours and continuous infusion over 24 hours respectively.
RESULTS: The standard and maximal dosing achieved PD target 4-38% and 21-68% respectively, when given over 0.5 hour. When each of the standard doses were given over 6 hours, the probability of achieving PD target increased to 18-63%. Continuous infusion over 24 hours offered the most promising PD target attainment of 65-81% (2x4 contingency table, $p<0.001$).
CONCLUSION: The current cefepime dosing recommendation has a low probability of achieving PD target predicting favorable outcome. The probability could be improved by using higher doses or extending drug infusion time.

213E. Pharmacokinetic modeling of oxaliplatin with and without 5-FU and radiation. *Patrick F. Smith, Pharm.D.,* Brent M. Booker, Pharm.D., Lakshmi Pendyala, Ph.D., Cynthia Gail Leichman, M.D., Joanne Berdzik, Margaret Muffley, Diane Noel, Michael Murphy, Lawrence Leichman, M.D.; Roswell Park Cancer Institute; University at Buffalo, Buffalo, NY.

PURPOSE: To characterize oxaliplatin PK alone and with fixed doses/schedules of 5FU/radiation in a phase I trial of esophageal cancer.
METHODS: Patients (n=19, 12M) received oxaliplatin 85 mg/m^2 on days 1 (2-hr infusion), 15 and 29 of a 6-week cycle, with continuous infusion 5FU (180 mg/m^2) beginning day 8 for 5 weeks, with external beam radiation; toxicity prevented dosage escalation. Plasma was collected and assayed (atomic absorption spectrophotometry) for platinum in ultrafiltrate after oxaliplatin alone (day 1) and after combination with 5FU/radiation (day 15), at 0, 0.25, 0.5, 1, 2, 3, 6, and 24 hours after infusion. Candidate PK models were fit to the data, with model discrimination by AIC. PK parameter estimates for each patient by maximum likelihood estimation, with final parameters determined by M.A.P. (maximum a posteriori) Bayesian estimation (ADAPT II). All PK data from days 1 and 14 co-modeled, with between-day parameter coefficients on clearance and volume, for determining inter-day differences.
RESULTS: Patients had a mean (CV%) age 66.5 (14) years, BSA 1.97 (18) m^2, creatinine clearance (ClCr) 61 (32) ml/min. Final PK model is linear, 2-compartment, and fit the data excellently (mean r^2=0.93, range 0.84-0.98). Mean (CV%) PK parameters: Steady-state volume of distribution (Vss) 231 (25) L; total clearance 11.8 (56) L/h; α and β half-lives 0.25 (15) and 17.8 (28) h. PK parameters did not differ between periods (p>0.05). Total clearance of oxaliplatin is associated with age and ClCr, and was predicted by a linear regression equation (r^2=0.76, p<0.001).
CONCLUSIONS: Oxaliplatin PK is linear and not significantly altered by coadministration of continuous infusion 5FU/radiation. ClCr and age are important predictors of exposure. The PK model is being utilized to design optimal sampling strategies and to link PK with pharmacodynamic endpoints of oxaliplatin therapy and gene expression markers.
Presented at the 92nd Annual Meeting of the American Association for Cancer Research, New Orleans, LA, March 24-28, 2001.

214E. Designing sparse sampling approaches to optimize indinavir (IDV) sampling times. *Robert DiCenzo,* Alan Forrest, Kathleen Squires, Scott Hammer, M. Fischl, V. Degruttola, Gene Morse, the ACTG 368 Protocol Team; University at Buffalo, Buffalo, NY; Adult ACTG, NIAID, Bethesda, MD.

PURPOSE: Develop optimal (OPT), maximally informative, sparse pharmacokinetic (PK) sampling strategies for IDV.
METHODS: Patients in ACTG 368 received efavirenz 600 mg daily and IDV 1000 mg TID or 1200 mg BID ± abacavir after failing zidovudine and lamivudine. A subset of patients had intensive (9 samples in one dose interval) PK at week 2. IDV was assayed using HPLC and modeled using an iterative 2-stage analysis. After determining the OPT 6 sampling times for each subject using a d-optimal sampling approach, efficiency was determined for the OPT 6 sampling times for the population. Precision of estimates of clearance was determined for the population's OPT 4, 3, 2, and two 1 sampling strategies.
RESULTS: 175 samples from 35 patients were analyzed to determine the 6 OPT sampling times for each subject. Efficiency for the population 6 sample strategy was median 0.767, mean 0.684, and SD 0.253. For clearance, the mean percent errors (SD) for the 4, 3, 2, 1 midpoint, and 1 trough sampling strategy were 0.950 (10.202), -7.775 (18.991), -0.431 (22.545), 1.452 (68.589), and -8.520 (42.187), respectively. OPT sampling approaches utilizing 4 (predose, 1, 2 and 6 hr post dose) samples provide accurate and precise estimates of IDV clearance. Three (predose, 1, and 6 hr post dose) and 2 sample (1 and 6 hr post dose) approaches perform reasonably well. One midpoint sample, and 1 trough sample strategies were badly biased and imprecise (see table).
CONCLUSIONS: Clearance of IDV can be measured with good precision using 6 or 4 OPT timed samples. Sampling strategies using 3 or 2 samples perform reasonably well whereas less than 2 samples were noninformative for estimating IDV PK parameters such as clearance.
Presented to the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

215E. Pharmacokinetics of lansoprazole with multiple oral and intravenous doses. James W. Freston, M.D., Ph.D., Mitchell A. Rosenberg, M.D., Janice S. Griffin, R.N., BSN, Nancy Lukasik, R.N., BSN, *Wei-Jian Pan, Ph.D.*; University of Connecticut Health Center, Farmington, CT; Parkway Research Center, Miami Beach, FL; TAP Pharmaceutical Products Inc, Lake Forest, IL; Abbott Laboratories, Abbott Park, IL.

PURPOSE: To evaluate the pharmacokinetics (PK) and safety of multiple oral and intravenous (IV) doses of 30 mg lansoprazole (LAN).
METHODS: This was an open-label, crossover study in which thirty-six healthy male and female subjects were randomly divided into groups to receive lansoprazole 30 mg daily for a total of five days either orally or via IV (30-minute infusion). Plasma samples were collected on days 1 and 5 and analyzed for pharmacokinetic parameters.
RESULTS: Differences observed for pharmacokinetic parameters were as expected due to the different routes of administration, however half lives between the two routes were similar. No clinically important changes were observed in the analyses of laboratory or vital sign results. Mean PK results for lansoprazole oral and IV administration were:

PK Parameters (total)	30 mg QD (Oral)		30 mg/30 min QD (IV Infusion)	
	Day 1	Day 5	Day 1	Day 5
C_{max} (ng/ml)	1027	1052	1814	1884
T_{max} (h)	1.7	1.5	0.5	0.5
AUC_{24} (ng-h/ml)	2876	3101	3463	3611
$t_{1/2}$ (h)+	1.24	1.20	1.15	1.19
MRT (h)	—	—	1.7	1.7
CL (L/h)	13.0†	12.9†	10.2	9.7
V_{ss} (L)	—	—	16.7	16.6

+ Harmonic mean, † CL/F

CONCLUSIONS: Like the lansoprazole oral capsule formulation, the pharmacokinetic profile of the lansoprazole 30 mg intravenous formulation does not change after repeated daily dosing and is not associated with changes in laboratory values or vital signs. Funded by TAP Pharmaceutical Products Inc.
Presented at the 66th Annual Scientific Meeting of the American College of Gastroenterology, Las Vegas, NV, October 19-24, 2001.

216E. Evaluation of acid suppression following intravenous lansoprazole and oral lansoprazole. James W. Freston, M.D., Ph.D., Mitchell A. Rosenberg, M.D., Janice S. Griffin, R.N., BSN, Nancy Lukasik, R.N., BSN, Wei-Jian Pan, Ph.D., Qiang Wang, M.S.; University of Connecticut Health Center, Farmington, CT; Parkway Research Center, Miami Beach, FL; TAP Pharmaceutical Products Inc, Lake Forest, IL; Abbott Laboratories, Abbott Park, IL.

PURPOSE: To compare the intragastric (IG) pH of lansoprazole (LAN) 30 mg administered intravenously (IV) with that of LAN 30 mg orally.
METHODS: This was an open-label, crossover study in which thirty-six healthy male and female subjects were randomly divided into groups to receive lansoprazole 30 mg daily for a total of five days either orally or via IV (30-minute infusion). Twenty-four hour intragastric pH was recorded on days 1 and 5 of each crossover period.
RESULTS: Post-dosing during hours 0-1 and 2-5 on day 1 and during hour 0-1 on day 5, the mean IG pH and the percentage of time pH was greater than 3, 4, 5, and 6 (hour 0-1 only) were significantly greater with the IV regimen than with the oral regimen. Mean intragastric pH values with oral and IV lansoprazole, determined by least squares mean estimates, were:

		Oral LAN	IV LAN (30 minutes duration)
Day 1			
	Total 24 Hours	4.75	4.86
	Hour 0-1	2.74	4.64†
	Hours 2-5	4.63	5.26†
Day 5			
	Total 24 Hours	5.25	5.36
	Hour 0-1	4.79	5.91†
	Hours 2-5	6.05	6.35

† significantly (p≤0.05) higher than the oral LAN regimen

CONCLUSIONS: The intravenous administration of lansoprazole raises the mean intragastric pH higher within a period of one hour and maintains the pH above 4 longer than the oral administration. The mean pH over the 24-hour post-dosing period does not differ between the two routes of administration. Funded by TAP Pharmaceutical Products Inc.
Presented at the 66th Annual Scientific Meeting of the American College of Gastroenterology, Las Vegas, NV, October 19-24, 2001.

217. Relationship between fluvoxamine pharmacokinetics and CYP 2C19 phenotype and genotype. *Michael W. Jann, Pharm.D., FCCP,* Troy L. ZumBrunnen, Pharm.D., Yusuf R. Kazmi, Pharm.D., Chad VanDenBerg, Pharm.D., Hiral D. Desai, Pharm.D., Donald J. Weidler, M.D., Ph.D., David A. Flockhart, M.D., Ph.D.; Mercer University, Atlanta, GA; Georgetown University, Washington, D.C.

PURPOSE: Genetic polymorphisms causing differences in metabolic activity in CYP 2D6 and 2C19 are well described. This study examined the pharmacokinetics of fluvoxamine (FLV) in poor (PMs) versus extensive metabolizers (EMs) of CYP 2C19.
METHODS: Healthy women and men (n=57; 14 Asian, 9 Afro-American, 34 Caucasian) volunteers were phenotyped for CYP 2C19 status based on the parent to metabolite (O/OM) ratio after a single dose of omeprazole 20 mg. PMs were identified based on a parent to metabolite (O/OM) ratio of ≥ 1.000. Selected EMs, based on a low O/OM ratio, and all PMs participated in the FLV testing phase. Blood samples for determination of FLV were obtained prior to and 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after a single dose of FLV 100 mg. Pharmacokinetic parameters of FLV were analyzed using WinNONLIN®. FLV pharmacokinetics between PMs and EMs were compared by Student's t-test.
RESULTS: Four PMs (3 Asian, 1 Caucasian) were identified with a mean

O/OM ratio of 1.335 ± 0.27 and nine EMs were selected with a mean O/OM ratio of 0.193 ± 0.079. Genotype analysis of the PMs revealed mutant *2 alleles on the CYP 2C19 gene supporting phenotype testing; all had normal CYP 2D6 genotype. Mean age and weight did not differ between the two groups. No differences in pharmacokinetics were found as follows:

	AUC (ng/ml·hr)	$t_{1/2}$ (hr)	Cmax (ng/ml)	Tmax (hr)
EMs	508.8 ± 193.2	15.1 ± 7.0	38.2 ± 12.1	5.3 ± 1.7
PMs	554.6 ± 367.1	15.6 ± 7.2	36.6 ± 13.6	6.3 ± 4.0
p value	0.34	0.40	0.38	0.22

CONCLUSIONS: FLV pharmacokinetics do not appear to differ significantly between PMs and EMs of CYP 2C19. FLV dosing in PMs or EMs of CYP 2C19 should not significantly be altered based upon CYP 2C19 genotype.

218. Celecoxib does not affect the anti-platelet activity of aspirin in healthy volunteers. *Keith D. Wilner, Ph.D.,* Margaret Rushing, Catherine Walden, Rebecca Adler, James Estes, James Lefkowith, M.D., Robert Noveck, M.D., Ramon Vargas, M.D.; Pfizer/Agouron, La Jolla, CA; Pfizer Inc, Groton, CT; Pharmacia Corporation, Skokie, IL; Clinical Research Center, New Orleans, LA.

BACKGROUND: Celecoxib is a novel COX-2 specific inhibitor for the treatment of the pain and inflammation of arthritis. Studies indicate that celecoxib (up to 1200 mg/day) has no effect on platelet aggregation or serum thromboxane (TXB_2) levels, which are predominantly mediated by COX-1. Up to now, there have been no platelet function studies in subjects receiving celecoxib and concomitant aspirin.
OBJECTIVE: To evaluate whether celecoxib, at therapeutic doses, alters the effect of concomitant aspirin on platelet function.
METHODS: In this double-blind, placebo-controlled study, 17 healthy volunteers (aged 18–48 years) received therapeutic doses of celecoxib (400 mg/day) or placebo for 5 days. On the fifth day of dosing, all volunteers received a single 325 mg dose of aspirin along with celecoxib or placebo. TXB_2 and platelet aggregation response to adenosine 5'-diphosphate (ADP), collagen and arachidonic acid were measured prior to the first dose of celecoxib or placebo (baseline) and on the fifth day of dosing, 2 and 8 hours post dose.
RESULTS: Aspirin decreased TXB_2 levels by approximately 100% from baseline in both the celecoxib and placebo groups. There was no significant difference in the $\%TXB_2$ inhibition between the two groups (placebo 99.36% vs celecoxib 99.01%, p=0.555). Likewise, there was no significant difference between celecoxib and placebo with respect to the effect of aspirin on % platelet inhibition due to ADP, collagen or arachidonic acid.
CONCLUSION: The results of this study demonstrate that celecoxib does not alter the effect of aspirin on TXB_2 or platelet aggregation.

219. Bioavailability of zonisamide capsule administered as sprinkle in healthy subjects. *Jaymin Shah, Ph.D.,* Rebecca Tupper, Janice Gross, Daniel Canafax, Pharm.D., Leslie Floren, Pharm.D.; Elan Pharmaceuticals, South San Francisco, CA.

PURPOSE: Evaluate the bioavailability (F) of the 100 mg zonisamide (ZNS) capsule sprinkled in applesauce compared with the intact 100 mg ZNS capsule.
BACKGROUND: ZNS is approved as Zonegran' capsule for adjunctive therapy in adults with partial seizures. The capsule may not be suitable for administration to all populations, especially to geriatric patients.
METHODS: This single-dose, open-label, two-period randomized crossover study with a 7-day washout assigned 20 subjects to treatment A or B: treatment A (test), a single 100 mg ZNS capsule sprinkled in applesauce and treatment B (reference), an intact 100 mg ZNS capsule. Serum ZNS samples collected pre-dose, and at hours 1, 2, 3, 4, 6, 8, 12,16, 24, 48, 96, and 120 post-dose were analyzed by HPLC – UV. Noncompartmental analysis was used to calculate pharmacokinetics (PK). The difference in F between the two treatments used 90% confidence intervals (CI) for the mean ratios of ln-transformed C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$.
RESULTS: ZNS PK parameters [mean (SD)] from treatments A and B (n=20) were: C_{max} (mg/ml):[8.12 (1.29) vs 8.12 (1.66)]; $AUC_{(0\text{-}t)}$ (µg•hr/ml):[51.8 (7.5) vs 52.3 (9.1)]; and $AUC_{(0\text{-}inf)}$ (µg•hr/ml):[67.9 (13.8) vs 71.1 (15.6)]. Ninety percent CI for the three PK parameters were: 93-105, 94-102, and 92-101, respectively. The two treatments showed no difference in PK and 90% CI were within 80-125%. Both forms of ZNS were safe and well tolerated.
CONCLUSIONS: ZNS F was similar following sprinkle in applesauce versus intact capsule. Patients who may have difficulty swallowing intact capsules now have an alternate mode of ZNS administration.

220. A population pharmacokinetic model of oral low dose methotrexate in patients with rheumatoid arthritis using computer based modeling program P-PHARM. *Nonglek Khu, Pharm.D.,* Ian C-K Wong, Ph.D., Henry Chrystyn, Ph.D., Sarah J. Bingham, MA, MRCP, Paul Emery, M.D., FRCP, Andrew C. Alldred, MRPharm.S.; University of Bradford, Bradford, United Kingdom; Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; University of Leeds, Leeds, United Kingdom.

OBJECTIVE: To establish a population pharmacokinetic model of oral low dose methotrexate (MTX) in patients with rheumatoid arthritis (RA) using P-Pharm software program.
METHODS: Twenty-four patients with RA received MTX from 5-25 mg/week orally were studied. Plasma samples were collected and measured by HPLC with fluorescence detection at time 0, 0.5, 1, 2, 4, 6, 8, 12 and 24-hour post dose. Data were analyzed by a non-linear mixed effect model to compute the population parameters and explore inter-individual variability of covariables: sex, age, weight, height, dose, creatinine clearance, C-reactive protein, rheumatoid factor and plasma viscosity.
RESULTS: Observed data were statistically fitted to the two-compartment model comparing to one-compartment ($p< 0.05$) with first order rate. The population parameters with inter-individual variabilities were expressed as mean and coefficient variation (%CV). These final estimates were clearance (CL) 6.62 L/h (33.2), central volume (Vc) 16.0 L (34.4), transfer rate constant from central to peripheral compartment (K12) 0.0722 h^{-1} (28.7), constant rate from peripheral to central (K21) 0.0990 h^{-1} (32.3), and absorption rate constant (Ka) 0.5478 h^{-1} (18.0). Only one covariable found to be significantly influenced on CL was dose ($p<0.01$). The goodness of fit was determined by Kolmogorov-Smirnov test showing the distribution of samples was not significantly different from normal (N(0,1)).
CONCLUSION: P-Pharm was useful to determine the population pharmacokinetic parameters with inter and intra-subject variabilities. The population model can be further used with Bayesian technique to investigate correlation between each individual's kinetic parameters and response of the oral MTX in RA with only few samples needed.

221. Solute removal characteristics of the CAHP-210 hemodialyzer: in vitro and in vivo comparison. *Kevin M. Sowinski, Pharm.D.,* Stephanie Magner, Pharm.D., Aroonut Lucksiri, Pharm.D., M.S., Richard J. Hamburger, M.D., Bruce A. Mueller, Pharm.D., Meri K. Scott, Ph.D.; Purdue University, Indianapolis, IN.

PURPOSE: The objective of this study was to determine the ability of an in vitro hemodialysis model to predict in vivo dialytic Cl with a CAHP-210 hemodialyzer.
METHODS: In vivo and in vitro studies were conducted. In the in vivo study, eight subjects with ESRD received IV vancomycin 15 mg/kg and gentamicin 1.5 mg/kg on the first study day. Two days later, at their next hemodialysis session, subjects were dialyzed with a CAHP 210 hemodialyzer with their usual dialysis operating procedures. To characterize the CAHP210 dialytic Cl of the solutes, blood samples were obtained prior to, at the midpoint of and at the end of hemodialysis. Dialytic Cl was determined by the Fick method. The blood flow rate was 410 ± 18 ml/min, dialysate flow rate was 625 ± 66 ml/min, and hematocrit was 37.7 ± 6.0% during the dialysis session. In the in vitro study, experimental hemodialysis was performed with a CAHP 210 dialyzer (n=6 dialyzers), 6 L of equine plasma containing urea, creatinine, gentamicin and vancomycin was pumped at 400 ml/min for 60 min, with a dialysate flow rate of 500 ml/min. Plasma and dialysate samples were obtained for the determination of dialytic Cl. In each study, concentrations of vancomycin and gentamicin, were determined by EMIT, and urea and creatinine by colorimetric assay. The relationship between in vivo and in vitro dialytic Cl was determined by regression analysis. Dialytic Cl values were compared between the in vivo and in vitro experiments using ANOVA.
RESULTS: Mean ± SD dialytic Cl values were:

Solute	In vivo dialytic Cl (mL/min) n=8 subjects	In vitro dialytic Cl (mL/min) n=6 dialyzers
Urea Nitrogen	202 ± 23*	305 ± 11.3
Creatinine	162 ± 21*	245 ± 11.9
Gentamicin	106 ± 13*	118 ± 7.02
Vancomycin	55.8 ± 9.7*	79.6 ± 11.3

*$p<0.05$, ANOVA; regression equation: in vivo dialytic Cl=0.59 • in vitro dialytic Cl + 20.6 ($r2=0.97$, $p<0.05$)

CONCLUSIONS: A strong and statistically significant relationship existed between in vitro and in vivo dialytic Cl values. In vitro dialytic Cl values were statistically significantly higher than the corresponding values in the in vivo experiments, although this difference was minimized with solutes of higher molecular weights.

222E. Characterization of UCN-01 specific binding to human α_1-acid-glycoprotein. *Judith A. Smith, Pharm.D., BCOP,* Jorge Cortes, M.D., Timothy L. Madden, Pharm.D.; M.D. Anderson Cancer Center, Houston, TX.

UCN-01 (U) is a potent inhibitor of cell cycle progression now being investigated as an antitumor agent. Preclinical studies have demonstrated significant (>95%) plasma protein binding (PPB) of U, majority to the α_1-acid-glycoprotein (AAG) fraction. Patients (n=14) enrolled in a phase II trial of UCN-01 + cytarabine at our institution experienced unexpected cardiovascular toxicity. In order to assess the variability and role of drug binding in this toxicity we examined, *in vitro*, the effects of both albumin (Alb) and AAG on U PPB. Equilibrium dialysis techniques were used to measure the free fraction of U in the presence of varying ratios of Alb and AAG. These solutions were spiked with U and dialyzed for 36 hours at 37°C against a Sorensen's solution using cellulose membranes with a MWCO of 12-14kD. Results (below) suggest while Alb and AAG play a role in UCN-01 PPB, AAG is more important. Varying AAG concentration resulted in the

largest changes in UCN-01 free fraction.

	Alb 3g/dl	Alb 4g/dl	Alb 5g/dl	Mean Percent UCN-01 Protein Bound (%)	STD (%)
AAG 50 mg/dl	85.26	88.52	89.24	87.67	2.12
AAG 100 mg/dl	90.35	92.44	91.63	91.47	1.05
AAG 200 mg/dl	97.94	97.81	96.6	97.45	0.74
AAG 300 mg/dl	99.69	99.82	100	99.84	0.16

With a mean PPB in human subjects of 97%, these data demonstrate that slight variations in plasma AAG concentration would result in large variations in free drug exposure.
Presented at the 102nd Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Orlando, FL, March 6-10, 2001.

223. Quantitation of SU5416, a novel antiangiogenesis agent, in human plasma by high-performance liquid chromatography. *Sonia S. Kim, Pharm.D., M.S.,* Michelle A. Rudek, Suoping Zhai, M.D., Ph.D., Min Kang, Pharm.D., M.S., Eunhee W. Woo, Pharm.D., Ph.D., Douglas Hanahan, M.D., William D. Figg, Pharm.D.; National Cancer Institute, Bethesda, MD; University of California, San Francisco, CA.

PURPOSE: A high-performance liquid chromatography assay was developed for quantitating SU5416, a novel antiangiogenic compound that acts as a potent and selective inhibitor of the Flk-1/KDR tyrosine kinase receptor, in human plasma using chrysin as the internal standard.
METHODS: The plasma samples were prepared using an acetonitrile precipitation. Analysis of SU5416 was performed with an Agilent 1100 series HPLC outfitted with a C8 precolumn and column (Agilent Zorbax 5 mm Eclipse XDB-C8, 4.6 x 150 mm). A gradient mobile phase consisting of acetonitrile and 0.01 M ammonium acetate was used for a run time of 14 minutes, with a 4-minute post run. SU5416 had a retention time of 10.8 minutes (detection at 440 nm); chrysin had a retention time of 9.8 minutes (detection at 268 nm). The limit of quantitation for SU5416 using this method was 10 ng/ml. A standard calibration curve from 10 ng/ml to 5000 ng/ml was used to quantitate SU5416 concentrations.
RESULTS: The interrun and intrarun mean percent errors for all three quality controls were less than 13% and 14%, respectively. Sample stability was established over 3 freeze/thaw cycles. The recovery of SU5416 was approximately 100%.
CONCLUSION: This validated HPLC method is suitable for determining SU5416 concentrations in human plasma. In addition, this assay method will be modified to measure SU5416 concentrations in tumor-bearing Rip1Tag2 mice.

224E. The pharmacokinetic effect and safety of zonisamide on steady-state phenytoin in patients with epilepsy. *William R. Garnett, Pharm.D., FCCP,* Allan R. Towne, M.D., William E. Rosenfeld, M.D., Jaymin Shah, Ph.D., Leslie Floren, Pharm.D.; Virginia Commonwealth University, Richmond, VA; Comprehensive Epilepsy Care Center, Chesterfield, MO; Elan Pharmaceuticals, South San Francisco, CA.

PURPOSE: Evaluate the effect and safety of zonisamide (ZNS) on phenytoin (PHT) pharmacokinetics (PK) at steady-state in patients with epilepsy.
BACKGROUND: ZNS, a novel sulfonamide derivative, is approved for adjunctive treatment of partial seizures. ZNS and PHT may interact because both utilize the CYP450 pathway. Earlier studies showed changes in ZNS half-life and clearance, but not in PHT PK parameters.
METHODS: This phase I, multiple-dose, open-label study included two baseline PK serum PHT measurements. While maintaining patient's usual dose of PHT, ZNS 100 mg QD was administered and then titrated to 200 mg BID over 3 weeks. On Day 35, both PK profiles were collected.
RESULTS: Fourteen subjects reached steady-state with less than 10% variability between average PHT pre-dose trough (C_{min}) and area under the curve (AUC) for two baseline measurements. Key PHT PK parameters [mean (SD)], measured on days -7, -1, and 35 (with ZNS, n=14) were: C_{max} (µg/ml): [20.0 (12.1) vs 20.5 (12.3) vs 20.5 (11.2)]; T_{max}: [4.7 (2.5) vs 5.5 (2.7) vs 5.4 (2.1)]; AUC $_{(0\text{-}12)}$ (µg•hr/ml): [218.5 (132.0) vs 206.5 (123.0) vs 216.4 (116.3)]. The mean PHT C_{max}, $T_{max,}$ and AUC at day 35 (with ZNS) were slightly increased relative to baseline measurements (without ZNS). Mean ZNS half-life (with PHT) was 28.3 (range 15.2-54.7). No serious adverse events or discontinuations were reported.
CONCLUSIONS: Steady-state dosing with ZNS did not significantly affect PHT PK parameters. As expected, the ZNS clearance increased and the half-life decreased in the presence of PHT, based on historical controls.
Presented at the 53rd Annual Meeting of the American Academy of Neurology, Philadelphia, PA, May 10, 2001.

225. Pharmacokinetics of cyclophosphamide and etoposide in plasma and cerebrospinal fluid during high dose administration for peripheral blood stem cell mobilization. *Norifumi Morikawa Ph.D.,* Teruaki Mori M.D., Hisanori Kawashima B.Sc., Tatsuya Abe M.D., Masaharu Takeyama Ph.D., Hidenori Kobayashi M.D.; Oita Medical University, Oita, Japan.

PURPOSE: The report investigates the pharmacokinetics of cyclophosphamide (CY) and etoposide (VP-16) in plasma and cerebrospinal fluid (CSF) during the high-dose administration for peripheral blood stem cell mobilization for two postoperative patients with recurrence of brain tumor.
METHODS: In patient A, we administered 2000 mg of CY for 3.75 hours. In patient B, we administered 600 mg of VP-16 for 5 hours over three days. We measured the plasma and CSF concentrations of CY and its metabolism nor-mustard (NM) by colorimetric assay method and those concentrations of VP-16 by HPLC.
RESULTS: In patient A, the plasma concentration of CY peaked at the end of infusion and then decreased in a bi-exponential decay pattern. The CSF concentration of CY peaked at the end of infusion, and then decreased in a mono-exponential decay pattern. The plasma concentration of NM peaked 2 hours after drug administration and then gradually decreased in a bi-exponential decay pattern. In patient B, the plasma concentration of VP-16 peaked at the end of infusion, and then decreased in a bi-exponential decay pattern. After the first treatment, the CSF concentration of VP-16 was detected 2 hours after the end of infusion, peaked at about 3 hours later, and decreased mono-exponentially. By model analysis, the lag times of each treatment were estimated as 6.68, 4.56, and 3.56 hours after the start of the first, second, and third infusions, respectively. The maximum CSF concentration of VP-16 was 0.08% that of the maximum plasma concentration.
CONCLUSION: The cytotoxicity of CY and VP-16 in CSF was low for the postoperative patients locally destroyed the blood brain barrier by surgery.

226. An investigation into the generalizability of a specific digoxin pharmacokinetic equation. *L. Gallard, M.Sc., M.R.Pharm.S.,* D. McRobbie, M.Sc., M.R.Pharm.S., J.G. Davies, Ph.D., M.R.Pharm.S.; Guy's and St Thomas' Hospital, London, England, United Kingdom; University of Brighton, Lewes Road, Brighton, England, United Kingdom.

PURPOSE: Pharmacokinetic equations have been postulated to predict steady state digoxin levels (Am J Hosp Pharm 1981;38:69-73). The equation described by Sheiner and colleagues (Pharmacokinet Biopharm 1977;5:445-78) was used to augment clinical judgment and reduce the need for blood tests in our institution. However, many of the patients for whom the equation was used would have fallen outside the original papers' inclusion criteria. We evaluated the generalizability of this equation to our population.
METHODS: A prospective, cross sectional study was performed on medical in-patients and anticoagulation clinic out patients. All patients taking digoxin were included, irrespective of renal function or other medicines. Relevant data was collected in order to perform the pharmacokinetic equation. This was compared to the digoxin level from a pre-dose blood assay. Patients not at steady state were excluded.
RESULTS: A total of 139 patients were included in the study. Only 24 patients (17%) had predicted digoxin concentrations within ± 10% of the measured serum concentration. 90 patients (65%) had a predicted digoxin level out side of ± 25% of the measured serum concentration. Discrepancies ranged from an over estimation of 1.62 micrograms/L to an under estimation of 1.86 micrograms/L.
DISCUSSION: The Sheiner equation was accurate only for a very small number of patients. There was neither a constant nor apparent clinical variables which corrected the estimated value. The original study excluded all patients taking interacting medicines, unstable renal function, hyper or hypokalemia, and altered thyroid function. In our study correlation was worst for those patients also receiving interacting medicines or antibiotics.
CONCLUSION: The equation described by Sheiner is not generalizable to our patient group. Serum concentrations should be measured to accurately assess therapeutic levels of digoxin.

227. The influence of pineapple and onion on the absorption of cyclosporine in animal study. *Hsiang-Wen Lin, M.S.,* Huei-Yann Tsai, Ph.D., P.D.L. Chao, Ph.D.; China Medical College Hospital, Taichung, Taiwan.

PURPOSE: The day-to-day variability in cyclosporine exposure is known in the transplant recipient, even no change of the regimen. The variety of food and various cooking method could probably affect cyclosporine or other medicine and influence blood level. To investigate what effect of pineapple and onion on cyclosporine absorption and disposition in rats first, will probably deal with some cyclosporine variation problems in human.
HYPOTHESIS: Pineapple has bromelain which digests cyclosporine, and onion has a great quantity of quercetin glycosides which is as an modulator of CYP 3A4 and P-glycoprotein, a drug efflux transporter, in in vitro studies. Therefore they affect cyclosporine concentration as feeding together in rats.
METHOD: Rats were given single dose of cyclosporine (Neoral® 1.25 mg/kg) with or without pineapple 3 ml or onion juice 2 ml by gastric gavage. Blood was withdrawn by cardiopuncture at 20 min, 40 min, 1, 3, 5, and 9 h. The cyclosporine blood concentrations were assayed using with fluorescence polarization immunoassay. Groups were compared by the unpaired t-test ($p<0.05$*).
RESULTS: After coadministration of pineapple or onion juice, the AUCs of cyclosporine were decreased by 59% and 74%, respectively.

	AUC $_{0\text{-}t}$ (ng.min/ml)	Difference (%) with Neoral	Cmax (ng/ml)
Neoral (n=5)	61631.8 ± 8742.4	-	240.0 ± 37.2
Neoral with Onion (n=7)	16068.2 ± 3759	-74%*	98.4 ± 16.5
Neoral with Pineapple (n=5)	25384.5 ± 8308.5	-58.8%*	133.8 ± 38.7

CONCLUSIONS: The results indicated that pineapple and onion markedly reduced the absorption of cyclosporine. It is suggested that avoiding coadministration of pineapple and onion with cyclosporine or requiring close monitoring if taking together. Moreover, the other food or herbs which might influence cyclosporine level or other medication should be further studied to help patients taking medication to ensure efficacy and safety.

228. The effects of postnatal age on gentamicin serum concentrations. *Eric B. Hoie, Pharm.D.,* Jennifer Knight, Pharm.D., Estella M. Davis, Pharm.D., Kristin Daniel, Pharm.D., Konstantine Manouilov, Ph.D.; University of Nebraska Medical Center; NHS Hospital, Omaha, NE.

PURPOSE: Determine if gentamicin serum concentrations obtained from newborns on day 2 of life versus days 3 or 4 resulted in significantly different pharmacokinetic parameters.
METHODS: A retrospective chart review of 268 infants who had peak and trough gentamicin serum concentrations determined on days 2, 3, or 4 of life. Blood samples were obtained 30 minutes before and 30 minutes after the 3rd or 4th dose. Elimination rate constant (K_e), serum half-life ($t_{1/2}$), and volume of distribution (Vd) were calculated using peak and trough concentrations. Gestational age, birth weight, gentamicin dose, peak concentration, trough concentration, and the day of life serum concentrations were determined were recorded for all infants. Infants were stratified into three groups based on gestational age (<30 weeks, 30-36 weeks, or >36 weeks). Birth weight, peak concentrations, trough concentrations, K_e, $t_{1/2}$, and Vd were compared by one way analysis of variance to determine if significant differences occurred when serum concentrations were determined on day 2 of life versus days 3 or 4.
RESULTS: The only significant differences were peak concentrations in infants <30 weeks GA (day 2; 6.9 ± 1.3 mg/L, day 3; 8.0 ± 1.5 mg/L, p=0.044) and trough concentrations in infants 30-36 weeks GA (day 2; 1.6 ± 0.4 mg/L, day 3; 1.4 ± 0.5 mg/L, p=0.01).
CONCLUSIONS: Calculated pharmacokinetic parameters using gentamicin serum concentrations determined on day 2 of life are not significantly different compared to calculated pharmacokinetic parameters using gentamicin serum concentrations determined on days 3 or 4. Determination of gentamicin serum concentrations and subsequent dosage changes can be done on day 2 of life in newborn infants.

229E. Pharmacodynamic profile of continuously infused piperacillin/tazobactam against *Pseudomonas aeruginosa* using Monte Carlo analysis. *Joseph L. Kuti, Pharm.D.,* Charles H. Nightingale, Ph.D., Richard Quintiliani, M.D., David P. Nicolau, Pharm.D.; Hartford Hospital, Hartford, CT.

PURPOSE: Piperacillin/tazobactam 9-13.5 g administration by continuous infusion (CI) routinely provides serum concentrations in excess of the susceptibility breakpoint (≤16) for most *Enterobacteriaceae*. Since the breakpoint for pseudomonas to this agent is considerably higher (≤64), the likelihood of obtaining adequate drug exposures with these P/T regimens against this bacterium is currently unknown. To determine the probability of obtaining adequate piperacillin concentrations above its MICs for pseudomonas in patients receiving CI, we utilized a Monte Carlo analysis.
METHODS: MICs of 620 pseudomonas isolates were determined by E-test and a distribution was constructed for the 548 susceptible isolates. Using a previously validated population pharmacokinetic equation, steady-state serum concentrations were estimated for 210 patients who received piperacillin/tazobactam via CI. A Monte Carlo simulation was performed to predict the probability of obtaining concentrations at the MIC, 2 x MIC, and 4 x MIC for patients infected with susceptible pseudomonas isolates.
RESULTS: MICs ranged from 0.09 to 64 with modal and median values of 3 and 4, respectively. Steady-state concentrations of 51.14 ± 17.52 mg/ml were estimated in our patient population. Pharmacokinetic data revealed a normal distribution suggesting the adequacy of the representative population. The level of certainty of obtaining concentrations at the MIC, 2 x MIC and 4 x MIC for piperacillin administered by CI was 96, 94, and 85%, respectively.
CONCLUSIONS: Despite concern for the place of CI piperacillin/tazobactam in the management of *Pseudomonas* infection due to the higher established breakpoint, our data suggest that the probability of achieving adequate drug exposure with our dosing regimens is exceedingly high for susceptible isolates.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

230. Liposomal tobramycin in the treatment of chronic pulmonary infections of *Pseudomonas aeruginosa*: a pharmacokinetic and efficacy study following multiple intratracheal administrations in rats. *Jean F. Marier, M.Sc.,* Jean Lavigne, M.Sc., Diane Potvin, M.Sc., Murray P. Ducharme, Pharm.D., FCCP; MDS Pharma Services, Ville St-Laurent, PQ, Canada; University of Montreal, PQ, Canada.

PURPOSE: The objective of this study was to determine the pharmacokinetics and the efficacy of free and liposomal tobramycin against *P. aeruginosa* in a model of chronic lung infection in rats.
METHODS: Rats were inoculated with 10^6 log colony forming units (CFU) of a mucoid variant of *P. aeruginosa* (PA 508) administered intratracheally. Three to five days after, the infection was verified by throat swabbing. Six days after inoculation, 600 µg of free or liposomal tobramycin were administered intratracheally for 4 consecutive days and rats (n=180) were sacrificed at multiple time points to assess pulmonary tobramycin concentrations by HPLC and residual amounts of *P. aeruginosa* (CFU). Pharmacokinetic parameters were calculated using a two-compartment model with NONMEM.
RESULTS: Mean (± SD) population elimination half-life (t1/2β) and exposure (AUCinf) of free tobramycin were 10.6 ± 3.4 h and 671 ± 173 µg/h, respectively. The pharmacokinetics of liposomal tobramycin was statistically different than that of free tobramycin, with a slower t1/2β (37.1 ± 17.5 h, p<0.01) and a higher exposure (6344 ± 2101 µg/h, p<0.01). On treatment days 1, 2 and 3, liposomal and free tobramycin displayed similar bactericidal activities. However, liposomal tobramycin displayed higher bactericidal activity (p<0.05 for ≥3 log CFU reduction) than free tobramycin on treatment day 4.
CONCLUSION: The encapsulation of tobramycin in liposomes markedly changed its pharmacokinetics and significantly improved its pulmonary antibiotic exposure and efficacy. These results support the hypothesis that repeated inhalation of liposomal tobramycin may improve the management of pulmonary infections of *P. aeruginosa*.

231. Construction of a gut-lung, dual absorption, first-pass model to describe the pharmacokinetics of beclomethasone dipropionate and its metabolites after administration by inhalation. *My My Trinh, B.Sc.,* Huy Ong, Ph.D., Malcolm R. Hill, Pharm.D., Jean-François Marier, M.Sc., Diane Potvin, M.Sc., Murray P. Ducharme, Pharm.D.; University of Montreal, Montreal, PQ, Canada; MDS Pharma Services Inc., Montreal, PQ, Canada; Propharmacon, San Diego, CA.

PURPOSE: To construct a pharmacokinetic (PK) model describing the plasma concentrations of beclomethasone dipropionate (BDP) and of two of its metabolites, beclomethasone-17-monopropionate (17-BMP) and beclomethasone (B), when given by inhalation to asthmatic patients.
METHODS: Two different doses (560 and 1120 µg) of BDP were administered to 30 patients. Plasma samples were obtained after BID administration for 7.5 days. Using generalized least-squares analysis with ADAPT II®, candidate PK models were compared by: 1) minimizing the values of the AKAIKE information criteria test (AIC), of the objective function and of the residual errors, 2) maximizing the median coefficient of determination and 3) by inspection of the quality of the fit on graphs.
RESULTS: Plasma concentrations of all analytes were best described simultaneously by a gut-lung dual absorption first-pass PK model. PK of the parent compound (BDP) and those of its metabolites were explained by a one-compartment and two-compartment model, respectively. First-pass and systemic biotransformation of BDP to 17-BMP and to its other metabolite, beclomethasone-21-monopropionate (21-BMP), was included. B is derived from 17-BMP and 21-BMP, and the two are also transformed to unknown products through other metabolic pathways.
CONCLUSIONS: The PK model takes into account the dual gut-lung absorption of the administered BDP dose and the metabolic events that could arise at each absorption site, as well as in the plasma. Using plasma concentrations of BDP and its metabolites, it is now possible to quantify the amount of drug delivered to the lungs and to assess the efficiency of a given delivery device.

232. Effect of ethanol administration on cocaethylene disposition. *S. Casey Laizure, Pharm.D.,* Naomi Gades, D.V.M., Timothy Mandrell, D.V.M., Robert B. Parker, Pharm.D.; University of Tennessee; St. Jude Children's Research Hospital, Memphis, TN.

PURPOSE: It is well know that the administration of ethanol reduces the clearance of cocaine (Coc) and results in the production of the active metabolite, cocaethylene (CE). CE and Coc are structurally similar, differing only by the replacement of a hydroxy group with a methoxy group on the cocaine molecule, suggesting they could potentially share common metabolic pathways that are inhibited by ethanol administration. The purpose of this study was to determine if the clearance of CE is affected by the co-administration of ethanol.
METHODS: This study was conducted in animals that were part of ongoing studies of the interaction between cocaine and ethanol. Six adult, male, conditioned, mongrel dogs received the following treatments on four separate study days: 3 mg/kg Coc, 3 mg/kg + 1 g/kg ethanol, 2.6 mg/kg CE, and 2.6 mg/kg CE + 1 g/kg ethanol. Ethanol was administered as a 40-minute intravenous infusion, and was given immediately before the administration of Coc or CE. Coc and CE were administered as a 5-minute intravenous infusion. Arterial blood samples were collected at baseline, 3, 5, 10, 15, 20, 35, 65, 125, 185, 240, and 420 minutes following the start of the Coc or CE infusion. Coc and CE plasma concentrations were determined by HPLC. Using WinNonlin (Pharsight, ver. 3.1), a two-compartment model with a weight of 1/predicted concentration was used to estimate pharmacokinetic parameters. A paired t-test was used to evaluate the differences in pharmacokinetic parameters between each drug given alone and with ethanol.
RESULTS: The following table gives the mean ± standard deviation for the clearance, $t_{1/2}$ (ß half-life, harmonic mean), and volume of distribution at

steady state for each of the four drug treatments.

	Coc	Coc+EtOH	CE	CE+EtOH
Clearance (L/min)	0.94 ± 0.20	0.72 ± 0.13†	0.84 ± 0.16	0.65 ± 0.0.17‡
$t_{1/2}$ (minutes)	54 ± 17.9	60 ± 8.5	56 ± 6.0	70.8 ± 8.6
Vss (L/kg)	2.80 ± 0.50	2.62 ± 0.46	2.70 ± 0.46	2.75 ± 0.36

† Coc + EtOH < Coc alone ($p<0.05$); ‡ CE + EtOH < CE alone ($p<0.05$)

In dogs pretreated with 1 g/kg of ethanol, the clearance of both Coc And CE decreased by 23%.

CONCLUSIONS: Ethanol inhibits the clearance of both Coc and CE to a similar extent. These results suggest that Coc and CE share a similar metabolic pathway that is inhibited by ethanol.

233. Pharmacokinetics of intravenous immunoglobulin (IVIG) in patients with hypogammaglobulinemia. *Mary H.H. Ensom, Pharm.D.,* Crystal Amos, B.Sc.Pharm., David Pi, MBBS, MBA, R. Robert Schellenberg, M.D.; University of British Columbia; St. Paul's Hospital, Vancouver, BC, Canada.

PURPOSE: Despite widespread use and a worldwide shortage of intravenous immunoglobulin (IVIG), its pharmacokinetic parameters are not well-defined. The purpose of this study was to characterize the pharmacokinetics of IVIG in patients with hypogammaglobulinemia.
METHODS: Fifteen patients with congenital or acquired hypogammaglobulinemia, who were on a chronic regimen (either every 3 or 4 weeks) of IVIG (Gamimune N 10%), participated in this open-label study. Following informed consent, patients received their usual dose of IVIG over a 2- to 4-hour period and underwent serial blood sampling pre-infusion and at 0.5h and 1,2,3 weeks (n=15) and 4 weeks (n=12) following the dose. Serum concentrations of IgG were measured by rate nephelometry and traditional compartmental and noncompartmental pharmacokinetic analyses performed.
RESULTS: Subjects consisted of 12 females and 3 males, aged 37 to 66 years (mean ± SD: 50.1 ± 9.7). Their mean dose of IVIG ranged from 15 to 35g (22.0 ± 4.6); 12 patients received their IVIG dose every 4 weeks and the remaining 3 received theirs every 3 weeks. All patients were deemed to be at steady state based on concordance between their IgG trough concentrations before 2 consecutive doses. Five patients had trough concentrations (range of 4.8 to 6.9 g/L) that were lower than the target trough concentration of 7 g/L; 2 patients had trough concentrations of 7.2 and 7.4 g/L, respectively; and the remaining 8 patients had higher trough concentrations (8.6 to 12.9 g/L). Pharmacokinetic parameters are listed in the following table:

	Cmax (g/L)	Cmin (g/L)	k (h^{-1})	t1/2 (h)	AUC (g*h/L)
Mean ± SD	14.7 ± 2.0	8.0 ± 2.2	0.00095 ± 0.00038	837.5 ± 297.6	6382.4 ± 1688.9

CONCLUSIONS: IVIG pharmacokinetics in patients with hypogammaglobulinemia demonstrate wide interpatient variability. Based on our preliminary findings and linear pharmacokinetic principles, we are now conducting a follow-up study that uses a dosing sliding scale to adjust patients' dosages to a common trough level of 7 g/L. Evaluation of the validity of the sliding scale and its impact on patient outcomes is expected to improve usage and prevent overuse of IVIG during an era of worldwide blood shortage.

Pharmacy Practice

234. Patients' interest in self-referral to pharmacotherapy clinic. *Keith D. Campagna, Pharm.D.,* Lee Ori, Pharm.D., Kem P. Krueger, Pharm.D., Ph.D.; Auburn University, Auburn, AL.

PURPOSE: Patients of a family medicine office practice were queried to determine their perceptions of 1) control of medical problems, 2) knowledge of medications, and 3) satisfaction with current sources and levels of information received about their medical problems and medications, in order to evaluate their interest in referral to a new in-house pharmacotherapy clinic.
METHODS: A one-page survey instrument, written at eighth-grade reading level, was developed and administered to waiting room patients during a four-week period.
RESULTS: One hundred-thirty one patients returned completed surveys. Seventy-five (57.3%) indicated they were either not, or only partially, in control of their medical problems. Forty-four (33.8%) were either not, or only somewhat, confident in their understanding of the medications they take. Forty-four (33.8%) had questions about either some or all of their medications. Forty-two (33.1%) had been told none, or some, of what they wanted to know about their medications. Forty-eight (36.6%) wanted more information about their medications. Twenty-nine (22.2%) wanted referral to pharmacotherapy clinic. Positive correlation coefficients were observed for: 1) confident understanding of medications and - feeling of control (r=0.52), - being told about medications by physician or nurse (r=0.57); and 2) desiring more information and wanting referral to pharmacotherapy clinic (r=0.48). Of the 75 patients who were not completely in control of their medical problems, 37 (49%) requested additional information. Only 17 (23%) of these same patients invited referral to pharmacotherapy clinic.
CONCLUSIONS: Self-referral does not appear to be a reliable source of patients for a new pharmacotherapy clinic.

235. Adherence to laboratory monitoring parameter recommendations for patients with diabetes mellitus depending on prescriber's residency year in training. *Patricia A. Rozek, Pharm.D.,* Simon Leung, Pharm.D; University of Cincinnati; University Hospital; Cincinnati, OH.

This study documented adherence to laboratory monitoring parameter recommendations by medical residents, based on the prescriber's year in medical residency training to 1) obtain a baseline understanding of physician adherence to national recommendations; 2) identify any opportunities for performance improvement in the ambulatory care setting; and 3) obtain a baseline understanding of the level of disease control for diabetes mellitus in the outpatient internal medicine clinic. Medical records of 113 patients requesting refills for diabetes medications during March 2001 were reviewed. Cholesterol panels, hemoglobin A1C levels and liver function test monitoring for thiazolidinedione therapy were documented. For patients of first year medical residents, 18/24 (75%) had cholesterol panels drawn within the past year, compared to 17/25 (68%) and 49/64 (77%) for patients seen by second and third year residents, respectively. Hemoglobin A1C levels were drawn within the past 6 months for 17/24 (71%), 19/25 (75%) and 50/64 (78%) of patients of first, second, and third year residents, respectively. Adherence to liver function test guidelines were disappointing. The data collected illustrated the majority of patients were monitored for both hemoglobin A1C and cholesterol panels. However, the results of the ordered tests demonstrated a need to improve care for the patients reviewed, regardless of prescriber year in training. Individual prescribers are being contacted to refer patients to the pharmacotherapy clinic for disease state management and a laboratory monitoring guideline sheet is being developed to assist in addressing the situation.

236. The method of measuring the improvement in clinical pharmacokinetics service by using Six Sigma method. Min Young Kim, R.Ph., Hwang Mi Park, R.Ph., Hyo Jung Park, R.Ph., *Kie Ho Sohn, Ph.D.,* Kyung Eob Choi., Pharm.D., Young Ha Park, Yok K. Soe, Pharm.D.; Samsung Medical Center; GE Medical System-Korea; Seoul National University Hospital, Seoul, Korea.

PURPOSE: To improve quality of clinical pharmacokinetics service (CPS), the speed and the accuracy of CPS, the key points of efficiency in CPS, were measured by using Six Sigma method.
METHODS: The speed of CPS was measured using total hours it took from blood sampling from a patient by a nurse to sending a CPS report to the patient's chart by a clinical pharmacist. Total hours were divided into blood sampling-to-sampling registering, sampling registering-to-C_{peak} result reporting, and C_{peak} result reporting-to-pharmacist's CPS report.
The accuracy of CPS was measured by evaluating the difference between expected C_{peak} and measured C_{peak}. Then the speed and the accuracy of CPS were expressed as σ level.
RESULTS: After the campaign for improvement by Six Sigma method, the speed was improved by 1.19σ (before and after the campaign; 0.56σ and 1.75σ, respectively) and the accuracy was improved by 0.7σ (before and after the campaign, -0.56σ and 0.14σ, respectively). Exact recordings of drug administration time, drug infusion time and blood sampling time were shown to have profound effects on the accuracy of CPS. The improvement in the speed and the accuracy of CPS could produce potential financial benefit of U.S. $15,300 a year.
CONCLUSION: There have not been studies on measuring and objectifying as numerical value for the speed and the accuracy of CPS; thus, Six Sigma method for improving efficiency in manufacturing process was applied to CPS process by expressing as σ level. The speed and the accuracy of CPS could be improved by tightly controlling many factors related to CPS efficiency.

237. Validation of instrument for characterizing pharmacists' interventions. *Boon Peng Lim, B.Pharm. (Hons),* Shyamala Narayanaswamy, B.Sc.Pharm., M.Sc.Pharm., Huei-Xin Lou, B.Sc.Pharm., M.Sc.Pharm.; Singapore General Hospital, Republic of Singapore.

PURPOSE: The aim of our study is to validate a previously published instrument (AJHP 1999;56:2444-50) for measuring the severity of medication errors and value of pharmacists' interventions in our local setting. The effect of staff seniority on the results was also studied.
METHODS: The instrument was modified for local use. Out of the 660 interventions in our outpatient pharmacies intervention database in January and February 2000, 92 were randomly selected with the intent to represent the range of possible types of interventions. These were evaluated by a panel of 8 pharmacists (4 senior, 4 junior).
RESULTS: The kappa values for severity-of-error and value-of-service ratings were 0.41 (0.33-0.48) and 0.14 (0.03-0.22) for senior pharmacists, and 0.56 (0.47-0.64) and 0.30 (0.22-0.44) for junior pharmacists respectively. The results showed that overall agreement for both scales was not good. This was mainly due to incomplete documentation about interventions. Agreement on the severity-of-error scale for junior pharmacists was better. This could be due to different areas of specialisation of senior pharmacists. Poor agreement in the value-of-service scale was mainly due to lack of documentation on who initiated the intervention (patient or pharmacist) and on the rationale for the

intervention. These result in different assumptions being made by each evaluator, and leading to inter-rater variance.
CONCLUSIONS: Both scales will be refined and revalidated before adoption for use locally. Pharmacists must be educated on the need for proper and complete documentation of their interventions.

238E. Evaluation of a new integrated discharge prescription form. Nicolas Paquette-Lamontagne, B.Pharm, M.Sc., *William McLean, Pharm.D.,* Lysanne Besse, B.Pharm, DPH, Jean R. Cusson, M.D., Ph.D.; Centre Hospitalier de l'Université de Montréal, PQ, Canada; University of Ottawa, Ottawa, ON; Université de Montréal, Montréal, QC, Canada.

PURPOSE: The lack of communication of changes to the patient's drug therapy during hospitalizations to on-going caregivers increases the risks of drug-related adverse events, in possibly 50% of patients. This prospective study was designed to determine if a new discharge prescription form integrating admission medications, in-hospital changes and discharge medications could enhance the accuracy of information in these patients' profiles in community pharmacies after hospital discharge.
METHODS: Patients admitted to Internal Medicine wards in February 1999 and discharged with a new integrated Discharge Prescription form (DPF) comprised the experimental group. Those admitted in January 1999 were discharged as usual and constituted the "usual discharge" (UD) control group. The goal was to determine the conformity rates of the community pharmacy patient's profile with the list prescribed at discharge.
RESULTS: 89 patients and 669 discharge medications were studied. Patient profiles had a higher conformity rate in the DPF group than in the UD group (82% vs 40%, p<0.001), and improvement could be attributed to higher conformity rates particularly for two criteria (medications stopped in hospital and dose changes in hospital). Based on a questionnaire, healthcare providers were satisfied with the new prescription form although pharmacists seemed more enthusiastic than physicians.
CONCLUSION: Integration of admission medications, in-hospital changes and discharge medications on a single form increases the conformity rates of community pharmacy patient profiles after hospitalization. This tool is well accepted by both pharmacists and physicians and will probably lead to a major decrease in drug-related problems.
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239. Providing care to non-English speaking patients: evaluation of community pharmacy resources. Kathy E. Sentena, Pharm.D., *Nanette C. Bultemeier, Pharm.D.,* Dean G. Haxby, Pharm.D.; Oregon State University, Portland, OR.

PURPOSE: There are more than 30 million U.S. citizens with limited English speaking abilities, and the number is expected to increase. Like other communities in the U.S., Portland, Oregon has a diverse population. Language barriers may compromise the delivery of pharmaceutical care, leading to inappropriate medication use. The purpose of this study is to evaluate the interpretation methods used to provide pharmaceutical care to non-English speaking patients in community pharmacies.
METHODS: A 21-question survey was mailed to 291 community pharmacies in the Portland metropolitan area. Information on the availability, utilization, and effectiveness of interpretation methods and pharmacy demographics was collected.
RESULTS: Preliminary analysis of the data (n=74, 36% of surveys returned as of 06/15/01), indicated that most pharmacies (97%) provide prescriptions to non-English speaking patients. Spanish, Vietnamese, Russian and Chinese were the most commonly encountered languages. Prescription labels or medication information sheets in languages other than English could be provided by only 54% and 59% of pharmacies, respectively, and only in Spanish in most cases. The most commonly used communication method was a family or companion interpreter, followed by prescription labels in the patient's language. Final results will be presented.
CONCLUSION: Many community pharmacies do not appear to have adequate resources to facilitate communication with non-English speaking patients. Community pharmacies rely heavily on family or companion interpreters, which have been found to have many limitations in other healthcare settings. Additional evaluation of communication between community pharmacists and patients with limited English skills, and the impact of language barriers on medication use is needed.

240. A comparison of latanoprost and dorzolamide as additional therapy in patients with glaucoma on β-blocker topical agents. Su-Jung Lee, M.S., *Sukhyang Lee, M.S., Pharm.D.*; Graduate School of Clinical Pharmacy; Sookmyung Women's University, Seoul, Korea.

PURPOSE: Glaucoma, a common cause of blindness, has been treated to reduce intraocular pressure (IOP) with many agents including β-blockers, parasympathomimetic agents, carbonic anhydrase inhibitors, and prostaglandins. β-blockers have been the most frequently prescribed monotherapy but some patients need additional agents to achieve target IOP. This study is to evaluate the additive effect of latanoprost or dorzolamide in patients with glaucoma on β-blockers.
METHODS: Glaucoma patients were eligible for this retrospective study when latanoprost (0.005% once daily in the evening) or dorzolarmide (2% twice daily) were administered in addition to the β-blockers. Exclusion criteria were the closed angle glaucoma, eye infection, wearing contact lenses, laser treatment within 6 months prior to the study regimen. Adequate IOP was defined as IOP less than 22 mm Hg on two occasions taken at an interval of at least 1 hour. IOP was measured with Goldmann tonometer at baseline, 1, 4, 8 and 12 weeks after treatment. Efficacy of IOP reduction was compared between latanoprost vs dorzolarmide by the combined β-blockers, betaxolol, timolol or carteolol. Assessment of ocular side effects included a slit-lamp evaluation of anterior chamber, a fundoscopy and a visual examination.
RESULTS: A total 78 eyes were included with 42 in the lantanoprost group and 36 in the dorzolamide group. IOP was reduced from 26.04 ± 5.40 to 16.04 ± 2.54 mm Hg (p<0.0001) in the latanoprost and from 25.57 ± 0.61 to 19.40 ± 1.30 mm Hg (p<0.001) until 12 week follow-up period without upward drift in IOP. With baseline IOP as covariate, IOP reduction (9.99 ± 3.27 mm Hg, 39.36%) in the latanoprost group was statistically significant compared to IOP reduction (5.75 ± 3.33 mm Hg, 22.75%) in the dorzolamide group (p<0.001). Among the combined β-blockers of betaxolol, timolol and carteolol, A combination of betaxolol reduced IOP the most effectively in both the latanoprost and the dorzolamide group. Both eye drops were generally well tolerated with similar incidence of total side effects (lantanoprost 42.8% vs dorzolamide 47.2%). The latanoprost group had conjunctival hyperemia (9, 21.4%), blurred vision (5, 11.9%) and the dorzolamide group had bitter taste (8, 22.2%), nausea (3, 8.3%) and burning sensation (3, 8.3%) as more frequent side effects. Iris pigmentation reported as more frequent side effect was not observed in the latanoprost group.
CONCLUSION: Addition of latanoprost or dorzolamide in patients on β-blockers caused a further reduction of IOP that may prove to be useful in treatment of glaucoma with more efficacy in the latanoprost group and similar incidence of total side effects.

Psychiatry

241. Olanzapine improves tardive dyskinesia in patients with schizophrenia. Bruce J. Kinon, M.D., *Virginia L. Stauffer, Pharm.D.,* Lynn Wang, M.S., Khanhn T. Thi, Pharm.D.; Eli Lilly and Company, Indianapolis, IN.

PURPOSE: Tardive dyskinesia (TD), a persistent abnormal involuntary movement disorder usually considered neuroleptic-induced, currently has no specific treatment. We report findings of the effects of olanzapine (OLZ) treatment upon TD.
METHODS: Eligible schizophrenic patients met restricted Research Diagnosis Tardive Dyskinesia criteria (restricted RD-TD) that specified for abnormal involuntary movements to be of at least moderate severity. Subjects received OLZ, 5-20 mg/day for 8 months within a double-blind design that included up to 2 medication reduction (75%) periods of 2 weeks duration. TD was assessed with the Abnormal Involuntary Movement Scale (AIMS) and psychopathology with the Positive and Negative Syndrome Scale (PANSS).
RESULTS: A significant reduction in mean AIMS Total score was demonstrated (n=95; BL=11.9; EP=7.5; p<0.001; LOCF). Nearly 70% of subjects no longer met the restricted RD-TD criteria after up to 8 months of treatment, with greater than 50% improving as early as 8 weeks. No statistically significant rebound worsening of TD was found during the blinded drug reduction periods. A significant improvement in the PANSS occurred (BL=68.2; EP=59.7; p<0.001, LOCF).
CONCLUSIONS: These data, suggesting an ameliorative, rather than masking effect, and the concurrent further improvement in clinical status suggests that OLZ may offer a potential treatment alternative for managing the schizophrenic patient with pre-existing TD.

242. Effect of gabapentin on plasma norepinephrine concentrations in healthy volunteers. *Sheri L. Hoyler, Pharm.D.,* Stanley W. Carson, Pharm.D., Michael Kotlyar, Pharm.D., Christina Hill-Zabala, Pharm.D., Elizabeth Johnson, Mary-Grace Lagomasino, R.Ph., Michael Golding, M.D.; University of North Carolina, Chapel Hill, NC; University of Minnesota, Minneapolis, MN; John Umstead Hospital, Butner, NC.

PURPOSE: In addition to its use as an anti-epileptic drug, gabapentin purportedly is an anxiolytic agent that has been usedIn addition to its use as an anti-epileptic drug to treat speaker's anxiety and alcohol withdrawal. Increased cardiovascular reactivity following public speaking and other mental stress testing has been associated with increased morbidity and mortality in those with coronary artery disease (CAD). We hypothesized that gabapentin can decrease anxiety and therefore, decrease cardiovascular stimulation, a potential benefit in those with CAD.
METHODS: Mental stress-induced cardiovascular responses were compared in 19 healthy subjects using a randomized, double-blind, crossover design with one dose of 900 mg gabapentin or placebo administered 2 hours prior to mental stress testing. Testing consisted of 30-minutes resting followed by a combined 18 minutes of impromptu speaking, tape-recorded speech replay, and oral arithmetic. Blood was sampled for plasma norepinephrine concentrations following the rest period, and during both the speech and math tests.

RESULTS: Plasma NE concentration significantly increased on gabapentin versus placebo in all conditions: resting (p=0.053), speech (p=0.040), and math (p=0.050). No differences were seen in resting or stress-induced blood pressures or pulses. However, subjects reported they were more relaxed (68.4%, NS) and felt they performed better (57.8%, NS) on gabapentin versus placebo.
CONCLUSIONS: Our results suggest that gabapentin may decrease subjects' perception of anxiety but does not lower blood pressure, heart rate, or catecholamine stress-responses. Indeed, plasma NE concentration was elevated after acute dosing of gabapentin. This elevation is concerning given the known deleterious effects of catecholamines in subpopulations of patients (e.g., those with CAD). Future studies are needed.

243E. Current trends in the management of antipsychotics in a long-term care dementia population: focus on adverse events. *Harlan Martin, R.Ph.,* CCP, FASCP, Michael P. Slyk, Pharm.D., FASCP, Sheila Deymann, R.Ph.; Pharma-Care, Inc., Clark, NJ; Pharmacotherapy Associates, Warren, OH.

PURPOSE: To assess the adverse events associated with the routine use of risperidone and olanzapine in long-term care patients with dementia and behavioral disturbances.
METHODS: An observational analysis was conducted at five consulting pharmacist sites across the U.S. Patients' average age was 82 years and Alzheimer's dementia was the primary diagnosis in 47%. Target behaviors for antipsychotic use included verbally and physically aggressive behaviors. The effects of risperidone and olanzapine were determined after 91 days of patient use.
RESULTS: At risperidone and olanzapine doses of 2 mg/d and 10 mg/d, respectively, the incidence of anxiety in both groups was lower than that reported in the product literature. Anxiolytic use tended to decrease in the risperidone group and did not change in the olanzapine group. The incidence of the anticholinergic event constipation (as measured by frequency of laxative use) was higher in the olanzapine than the risperidone group (19% versus 4%; p<0.01). Falls were recorded in 10% of olanzapine patients versus 4% of risperidone patients (p<0.01).
CONCLUSIONS: The lower incidence of adverse events (anxiety, anticholinergic effects, and falls) with risperidone suggests that low doses of this agent may be a favored antipsychotic for use in the long-term care setting.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

244E. Psychosis of Alzheimer's disease: evidence from community-dwelling and nursing-home patients. *Rick Martinez, M.D.,* Judy Napolitano, R.N., Paul Kershaw, M.D., Akiko Okamoto, Sc.D.; Janssen Pharmaceutica Products, L.P., Titusville, NJ.

PURPOSE: Determine whether there is a definable psychotic syndrome in elderly patients with Alzheimer's disease (AD) and other dementias.
METHODS: Data were derived from a 5-month study of community-dwelling patients with mild to moderate dementia (study 1) and a 3-month study of nursing-home residents with severe dementia (study 2). Psychosis was defined according to scores on the Neuropsychiatric Inventory or the Behavioral Pathology in Alzheimer's Rating Scale.
For the galantamine data, the presence of psychosis was determined from the NPI scores on the delusion and hallucination subscales. A score of 4 or greater, indicating generally that, over the previous two weeks, the frequency of delusions and hallucinations are at least once per week and are distressing and disruptive, was criteria for psychosis.
RESULTS: Of the 285 placebo patients in study 1, all had AD, and of the 162 placebo Inpatients in study 2, 84% had AD, 16% other dementia to complete. In study 1, 12% of patients showed psychosis before the baseline assessment and 64% had a persistent psychosis for at least 1 month; 12% of patients without psychosis at baseline developed psychosis. In study 2, 63% of patients had psychosis at baseline, which persisted for at least 2 weeks in 75%; 17% of patients without psychosis at baseline developed psychosis. Persistent or continuous psychosis was present in 29% of the patients for 12 weeks.
CONCLUSIONS: The data support the concept that psychosis of dementia is a clinically definable entity, across the spectrum of AD from mild to severely impaired patients.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

245. Relationship of length of stay to atypical antipsychotic use among psychogeriatric inpatients with dementia of the Alzheimer's type. *Marcia Rupnow, Ph.D.,* George Papadopoulous, B.Sc., William Edell, Ph.D.; Janssen Pharmaceutica Products, L.P., Titusville, NJ.

OBJECTIVE: To examine the inpatient length of stay (LOS) associated with antipsychotics (olanzapine, quetiapine, and risperidone) in patients with Dementia of the Alzheimer's Type (DAT).
METHOD: Data were obtained from the CQI+SM Outcomes Measurement System, which tracked patients admitted to inpatient programs in 111 general hospitals across 33 states between 1997-1999. A Medication Usage Questionnaire was used to track prescribed medications. LOS was captured from the medical record. We only included patients who were taking one antipsychotic agent.
RESULTS: Group sizes at discharge were: olanzapine (n=66), quetiapine (n=41), and risperidone (n=147). Groups did not differ at admission in age, education, marital status, level of depression, and overall physical and mental health status. Patients taking risperidone (12.3 days) at discharge had a shorter LOS than those taking quetiapine (16.4 days; p<0.02) or olanzapine (14.9 days; p<0.08), with little evidence for different clinical outcomes.
CONCLUSIONS: Patients taking risperidone were hospitalized, on average, four days less than patients taking quetiapine, and about two and a half days less than those taking olanzapine. Using a conservative estimate of $492.00 for cost per day in the hospital, these findings suggest that savings per patient for those prescribed risperidone was $1279.20 to $2017.20 as compared with olanzapine or quetiapine, respectively.

246. Olanzapine versus haloperidol in transitioning from intramuscular (IM) to oral therapy. Padraig Wright, M.R.C.Psych., M.D., Karena Meehan, M.R.C.Psych., M.D., Martin Birkett, B.Sc., Stacy David, Ph.D., Cindy C. Taylor, Ph.D., Philip Morris, B.Sc.Med., M.B.B.S., Ph.D., Alan Breier, M.D., *Virginia L. Stauffer, Pharm.D., BCPS*; Eli Lilly and Company Ltd., Surrey, United Kingdom; Institute of Psychiatry, University of London, United Kingdom; Eli Lilly and Company, Indianapolis, IN; Gold Coast Hospital, Southport, Queensland, Australia.

OBJECTIVE: The primary objective of this study was to determine if, for up to 4 days following the transition from the IM to the oral formulation, olanzapine is comparable to the typical antipsychotic haloperidol in sustaining alleviation of agitation, with a more favorable safety profile.
METHODS: Acutely agitated inpatients with schizophrenia who had been treated with IM olanzapine (n=122) or IM haloperidol (n=116) over a 24-hour period were entered into a 4-day oral treatment period with the same medication (5 to 20 mg/day). Baseline to endpoint change on the PANSS-EC was the primary efficacy measurement. Safety was assessed by collecting adverse events, baseline to endpoint change and treatment-emergent extrapyramidal symptoms, anticholinergic use, and ECG QT_c interval changes.
RESULTS: Significant and similar baseline to endpoint reductions in agitation were observed for IM olanzapine and IM haloperidol during the 24-hour IM period on the PANSS-EC. Continued PANSS-EC score improvement was observed over the 4-day oral period for both treatment groups, with no significant between-group difference. Significantly more oral haloperidol-treated patients spontaneously reported treatment-emergent acute dystonia, extrapyramidal syndrome, and akathisia compared with oral olanzapine-treated patients. There were no significant between-group differences in baseline to endpoint EPS change. Criteria for akathisia was met significantly more for oral haloperidol than oral olanzapine, and significantly more haloperidol patients used anticholinergic medications. There were no between-group significant differences in QT_c interval changes.
CONCLUSIONS: IM olanzapine and IM haloperidol effectively reduced acute agitation in schizophrenia over 24 hours. The reduction in agitation was sustained for up to 4 days following the transition to oral therapy with both olanzapine and haloperidol. During the oral treatment period, olanzapine demonstrated a more favorable safety profile than haloperidol.

247E. Nizatidine may ameliorate weight gain during olanzapine treatment. Alan Breier, M.D., Yoko Tanaka Ph.D., Suraja Roychowdhury Ph.D., W. Scott Clark, Ph.D., *Virginia L. Stauffer, Pharm.D.*; Eli Lilly and Company, Indianapolis, IN.

OBJECTIVES: Weight gain is an adverse event reported during treatment with olanzapine and other psychotropics. Nizatidine is a histamine (H)-2 receptor blocker and has been reported to reduce weight gain during olanzapine treatment. This double-blind study evaluated the role of nizatidine in ameliorating weight gain during olanzapine treatment for up to 16 weeks in patients with schizophrenia and related disorders.
METHODS: After an initial screening period of 2-9 days, 142 patients were randomized to receive olanzapine (5-20 mg)+ placebo, olanzapine (5-20 mg) + nizatidine (150 mg BID) or olanzapine (5-20 mg) + nizatidine (300 mg BID). 132 patients were included in this interim analysis. Patients were followed for change in weight (primary objective) and effects on primary psychopathology and safety measures.
RESULTS: Patients treated with olanzapine + nizatidine (300 mg BID) had gained significantly less weight at week 16 than did those treated with olanzapine and placebo (2.76 vs 5.52 kg, p<0.02). This significant amelioration was seen as early as week 3 and continued throughout the 16 weeks. Additionally, in the nizatidine 300 mg BID group, weight gain appeared to plateau by week 8. Most patients appeared to benefit to some extent, as seen by a shift of the weight gain distribution curve to the left; a range of weight gain was still seen (-2.3-10.5 kg). Mean olanzapine dose was 10.4 mg (placebo group) vs 12.5 mg (nizatidine 300 mg group). Nizatidine was well-tolerated and overall clinical outcomes were not adversely affected.
CONCLUSION: Nizatidine 300 mg BID may ameliorate weight-gain during olanzapine treatment.

Presented at the Annual Meeting of the College of Psychiatric and Neurologic Pharmacists, San Antonio, TX, March 24-27, 2001.

248E. A pharmacoepidemiological study of diabetes mellitus and antipsychotic treatment in the United States. Patrizia Cavazzoni, M.D., Kenneth Kwong, M.D., Kenneth Hornbuckle, Ph.D., David Hutchins, MHSA, Lois Jovanovic, M.D., John Buse, M.D., Ph.D., *Angela Hill, Pharm.D.*; Eli Lilly and Company, Indianapolis, IN; University of Ottawa, Ottawa, ON, Canada; Advance PCS, Scottsdale, AZ; Sansum Medical Research Institute, Santa Barbara, CA; University of North Carolina, Chapel Hill, NC.

PURPOSE: To determine the relative risk of diabetes mellitus (DM) while receiving antipsychotic therapy.
METHODS: Patients starting antipsychotic therapy on a single antipsychotic were identified by prescription claims in the AdvancePCS' database. DM was identified by claims for anti-diabetic medications and DM incidence was determined in the following cohorts: general PCS patient population, combined conventional antipsychotics, haloperidol, thioridazine, combined atypical antipsychotics, olanzapine, risperidone, quetiapine, and clozapine. Hazard ratios (HR) of DM risk were determined in antipsychotic cohorts relative to the general PCS patient population and to each other.
RESULTS: The HRs of DM during treatment with conventional and atypical antipsychotics compared to the general PCS population were 3.5 ($p \leq 0.0001$) and 3.1 ($p \leq 0.0001$), respectively. The HRs of antipsychotic cohorts were; quetiapine (1.7; p=0.002), olanzapine (3.0; $p \leq 0.0001$), haloperidol (3.1; $p \leq 0.0001$), clozapine (3.3; p=0.007), risperidone (3.4; $p \leq 0.0001$) and thioridazine (4.2; $p \leq 0.0001$). When conventional and atypical cohorts were compared, there was no significant difference in DM risk (HR=0.966; p=0.6). Compared to the haloperidol cohort, a statistically significant increased DM risk was observed in the risperidone cohort (HR=1.2; p= 0.04). While the risk of DM was greater in the risperidone compared to the haloperidol cohorts (HR=1.2; p=0.04), there was no significant difference in DM risk on comparison of the olanzapine and risperidone cohorts (HR=0.9; p=0.23).
CONCLUSIONS: An increased risk of DM compared to the general population was observed during treatment with conventional and atypical antipsychotics. However, a comparable risk of DM was observed between atypical and conventional antipsychotic cohorts.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

249. Use of atypical antipsychotics and the incidence of diabetes: evidence from a claims database. Maureen J. Lage, Ph.D., Jason E. Kemner, MPH, *Angela Hill, Pharm.D.*; Eli Lilly and Company, Indianapolis, IN.

OBJECTIVE: Compare the incidence of diabetes between patients initiating treatment with typical or atypical antipsychotics.
METHODS: Retrospective analysis of the IMS Lifelink™ claims database identified 6,758 enrollees with the following characteristics: (1) age 18-65; (2) initiated on typical (n=3,381) or atypical (n=3,377) between October 1996 and December 1998; (3) no use of antipsychotics for six months prior-initiation; (4) not classified as diabetic (i.e. no diagnosis of diabetes or receipt of any diabetic medication for one year prior-initiation).
Logistic regressions were used to estimate odds ratios (OR) of a diagnosis of diabetes or use of any diabetic medication in the one year post-initiation, controlling for age, gender, and regional differences.
RESULTS: Higher probability of becoming diabetic was not evident following initiation on atypicals (mean duration of therapy 135 days) compared to typicals (mean duration of therapy 84 days; OR=1.032; p=0.825) or initiation on olanzapine (OLZ) or risperidone (RIS) compared to typicals (OR=0.977, 1.170; p=0.899, 0.35, respectively. The probability of developing diabetes was less in patients treated with OLZ (mean dose 9.01 mg/day) than in patients treated with RIS (mean dose 2.37 mg/day; OR=0.834; p=0.277), although the difference was not statistically significant.
CONCLUSION: The probability of developing diabetes was no more likely following treatment with atypicals than typicals. Within atypical use, the probability of developing diabetes was less during treatment with OLZ than with RIS, although the difference was not statistically significant.

250. Concomitant use of antipsychotics and cytochrome P450 3A4-metabolized medications in the treatment of schizophrenia. *Haya Ascher-Svanum, Ph.D.,* John S. Kennedy, M.D., David Lee, Ph.D., Merle Haberman, MHA, Shonda Foster, Pharm.D.; Eli Lilly and Company, Indianapolis, IN; Caremark/Protocare Sciences, Herndon, VA.

PURPOSE: Antipsychotics are extensively metabolized by cytochrome P450 enzymes, thus establishing the potential for pharmacokinetic drug-drug interaction when coadministered with other drugs. The purpose of this analysis was to assess the prevalence and utilization pattern of concomitant CYP3A4-metabolism inhibiting medications in schizophrenia patients who were treated with antipsychotics.
METHODS: This retrospective cohort study is based on proprietary managed care claims database representing a large, geographically diverse US population. Health care administrative claims, covering 1-year period (1999), were used to identify schizophrenia patients (n=1938) who were treated with antipsychotics and co-prescribed medications that were CYP3A4 inhibitors.
RESULTS: 26% of the patients experienced concomitant use of at least one CYP3A4 inhibitor medication. Most (73%) of the concurrent inhibitors were confined to four drugs (fluoxetine, erythromycin, nefazodone and nifedipine). Utilization patterns differed across gender and age categories but were similar for patients treated with classical and novel antipsychotics.
CONCLUSIONS: One fourth of the schizophrenia patients in this study used concomitant CYP3A4 inhibitor medications and antipsychotic drugs. A number of atypical antipsychotics (e.g., ziprasidone, quetiapine) are dependent for clearance upon metabolism by CYP3A4 enzymes. The combined therapies of such antipsychotics with CYP3A4 inhibitors could alter their pharmacological effects and potentially lead to various adverse effects. Further studies are needed to determine whether dosing antipsychotic medications that are metabolized by the CYP3A4 enzyme will require added monitoring and slow titration in order to minimize potential adverse drug-drug interactions when concurrent CYP3A4 inhibitors are present.

251E. The Texas Medication Algorithm Project (TMAP): outcomes for persons with major depressive disorder. *M. Lynn Crismon, Pharm.D.,* Madhukar H. Trivedi, M.D., A. John Rush, M.D., T. Michael Kashner, Ph.D., Marcia G. Toprac, Ph.D., Melanie M. Biggs, M.D., Kathy Shores-Wilson, Ph.D., Thomas J. Carmody, Ph.D., Steven P. Shon, M.D.; University of Texas, Austin, TX; University of Texas Southwestern Medical Center, Dallas, TX; Texas Department of Mental Health and Mental Retardation, Austin, TX.

PURPOSE: TMAP is an evaluation of an algorithm based disease management program for treatment of the seriously mentally ill in the public mental health sector. This poster presents the clinical outcomes of those patients with major depressive disorder (MDD).
METHODS: Interventions were implemented by clinic, with intervention clinics (ALGO), pure controls (τnonALGO), and controls within an ALGO clinic for another disorder (τinALGO). A change in antidepressant medication qualified patients for enrollment. Comprehensive outcomes assessments were performed by independent evaluators at baseline and every 3 months for at least 1 year.
RESULTS: A total of 548 patients with MDD were entered into one of the 3 groups. Outcomes were identical in the two τ groups. Since the ALGO group had higher baseline depression scores, 175 patients from ALGO were matched with 175 patients from the combined τ groups to avoid regression to the mean in favor of ALGO. Hierarchical linear models estimated treatment effects based on change from baseline scores, adjusted for multiple baseline factors. Mean baseline scores on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C30) were 41.4 ± 9.4. Both of the groups improved during the study ($p<0.0001$). Over the study period, the ALGO group had significantly fewer symptoms by an average of 4.55 IDS-C30 total points ($p<0.004$) than the matched τ group. ALGO was also superior to τ on improvement in the SF-12 mental function ($p<0.046$).
CONCLUSION: The TMAP disease management intervention over the course of one year was superior to τ in the treatment of patients with MDD.
Presented at the 39th Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 12, 2000.

252E. A comparison of expenditures by indigent patients continuously treated with atypical antipsychotic agents within a behavioral health organization in Texas. *Michael P. Johnsrud, Ph.D.,* M. Lynn Crismon, Pharm.D., Ann Thompson, MBA, BSN, Amy Grogg, Pharm.D.; The University of Texas at Austin, Austin, TX; Janssen Pharmaceutica, Titusville, NJ.

BACKGROUND: On July 1, 1999, Texas began enrolling one region of indigent (non-Medicaid) mental health patients into a managed mental health pilot program, with the goal of providing greater access to and more continuity of mental health services.
OBJECTIVE: This study compares prescription and mental health services expenditures for indigent schizophrenia patients treated with one of two atypical antipsychotic agents.
METHODS: Prescription and mental health service records were extracted from the administrative database of a regional behavioral health organization for the period of July 1, 1999 through June 30, 2000. Schizophrenia-related expenditures were collected for patients continuously prescribed either risperidone or olanzapine.
RESULTS: No significant differences between risperidone (n=57) and olanzapine (n=84) were shown in mean age (43.4 vs 43.8, p=0.813), percent female (36.8% vs 40.5%, p=0.664), or ethnicity, non-white (43.9% vs 42.9%, p=0.280). Mean total prescription costs were significantly lower for risperidone patients ($2347 vs $3502, $p<0.001$). Risperidone patients also had significantly lower schizophrenia-related inpatient and outpatient medical costs ($715 vs $1445, p=0.020) and total overall schizophrenia-related expenditures ($3062 vs $4947, $p<0.001$).
CONCLUSION: Indigent schizophrenia patients within a Texas behavioral health organization continuously treated with risperidone, as compared to olanzapine, had significantly lower annual schizophrenia-related prescription and medical expenditures.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

253. Increased lithium dose requirement in patient with hyperglycemia. *Monica Cyr, Pharm.D.,* Melanie Guia, M.D., S. Casey Laizure, Pharm.D.; Lakeland Regional Medical Center, Lakeland, FL; VAMC, Memphis, TN; University of Tennessee, Memphis, TN.

PURPOSE: Lithium is filtered by the kidneys and reabsorbed exclusively in the proximal tubule. Thus, drugs that affect proximal tubule fluid dynamics such as thiazide and osmotic diuretics will alter lithium renal clearance. The purpose of this case is to alert clinicians to the fact that hyperglycemic states can also alter proximal tubule fluid dynamics resulting in a change in the renal clearance of lithium.
METHODS: Data was collected from a persistently hyperglycemic patient in whom lithium plasma concentrations (Cp_{Li}) were low despite receiving doses that normally achieved therapeutic lithium plasma concentrations. The lithium doses, lithium plasma concentrations, and blood glucose concentrations occurring over a 56-day hospital admission were evaluated to determine if high blood glucose concentrations appeared to affect the lithium plasma concentration. The lithium dose required to increase the lithium plasma concentration by 0.1 mEq/L was calculated [$LiDose_{0.1}$ = (0.1) (LiDose)/Cp_{Li}]. A linear regression was performed with $LiDose_{0.1}$ as the dependent variable and blood glucose concentration as the independent variable.

Day	LiDose	Cp_{LI}	BGC	$LiDose_{0.1}$
8	900	0.30	255	300
16	1800	0.33	253	545
26	2400	1.03	250	233
32	2400	0.60	177	400
39	2400	1.16	106	188
43	2400	1.28	136	188
50	1800	0.90	263	200

RESULTS: Over the course of the patient's hospitalization 50 blood glucose concentrations and 8 lithium plasma concentrations were determined. The lithium dose was increased from 900 mg/day up to a maximum of 2400 mg/day. The table gives the lithium doses (LiDose) and blood glucose concentrations (BGC) associated with each of the 8 lithium plasma concentration determinations (Cp_{LI}) and the calculated lithium dose required to increase the plasma concentration by 0.1 mEq/L ($LiDose_{0.1}$). A linear regression of $LiDose_{0.1}$ versus blood glucose concentration resulted in an r^2=0.58.
CONCLUSIONS: Though there is a theoretical basis for hyperglycemia causing an increased renal clearance of lithium due to hyperglycemic-induced osmotic diuresis, there are no reports in the clinical literature of increased lithium dose requirements in patients who are hyperglycemic. This case report suggests that hyperglycemia can significantly increase lithium clearance requiring dosage adjustments in order to maintain therapeutic plasma concentrations.

254E. Evidence of efficacy of risperidone in schizophrenia. John M. David, M.D., *Nancy Chen, M.S.*; Psychiatric Institute of Chicago, Chicago, IL.

BACKGROUND: Stimulated by the need pointed out by Dawkins, et al (1999) and Remington and Kapur (2000) to develop a clinical profile of the new atypical antipsychotic drugs and by the critiques of Mattes (1997, 1998), analyses were performed to define the clinical profile of risperidone.
METHODS: Data from the North American risperidone trial were reanalyzed and a meta-analysis of the results of 11 controlled trials of risperidone was performed.
RESULTS/CONCLUSIONS: Risperidone was superior to haloperidol to an equal degree in patients with and without the deficit syndrome, in patients with paranoid and nonparanoid schizophrenia, in treatment-resistant and treatment-responsive patients (patients hospitalized for longer and shorter periods), and in patients with or without weight gain. Moreover, risperidone was more effective than haloperidol on symptoms nonresponsive and responsive to haloperidol; its effects on negative symptoms were independent of its effects on extrapyramidal symptoms; and it was found to have a beneficial effect on depression in schizophrenia. According to the meta-analysis, risperidone was consistently more effective than conventional antipsychotics in the treatment of both positive and negative symptoms.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

255. Patient characteristics associated with non-prescription drug use in intentional overdose. *Stephen J. Shalansky, Pharm.D., FCSHP,* Andre Lo, B.Sc.Pharm., Yitzchak Hollander, M.D., Marianna Leung, B.Sc.Pharm., Janet Raboud, Ph.D.; St. Paul's Hospital and Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada.

BACKGROUND: Over-the-counter (OTC) medications are freely available to suicidal patients despite their potential lethality and common use in suicide. Identifying patient characteristics independently associated with the use of OTC medications in intentional overdose may provide evidence for precautionary measures in specific populations.
METHODS: Health records were reviewed for a random selection of patients admitted to an urban academic center for intentional drug overdose between August 1, 1997 and July 31, 1998. Data was collected on diagnoses, psychiatric care, demographics, living situation, and medication use. Univariate and multivariate analyses were carried out to identify potential risk markers for OTC medication overdose.
RESULTS: Of the 95 patients included in the analysis, 59 (62%) had documented previous suicide attempts. OTC medication was used in 28 (29.5%) of overdoses, with acetaminophen being involved in 18 (64%) of these cases. Independent risk markers for overdose using OTC medication identified in the multivariate model included no possession of prescription medications at the time of overdose (OR 4.73; 95% CI 1.3, 7.4; p=0.02) and older age (OR 1.78 per decade; 95% CI 1.0, 3.1; p=0.04). Patients with a diagnosis of substance abuse had a lower risk (OR 0.1; 95% CI 0.03, 0.50; p<0.01).
CONCLUSIONS: Clinicians and family members dealing with suicide-prone patients should be aware that intentional drug overdose leading to hospital admission commonly involves OTC medication, especially acetaminophen. Older patients, and those not possessing prescription medication may be more likely to choose OTC medication for intentional overdose, thus precautions should be considered in these populations.

256E. Efficacy of risperidone add-on to mood stabilizers in acute and continuation treatment of mania. Lakshimi Yatham, M.D., *Carin Binder, B.Sc.,* RIS-CAN-25 Study Group; University of British Columbia, Vancouver, BC, Canada; Janssen-Ortho, Inc., Toronto, ON, Canada.

OBJECTIVE: To determine efficacy and safety of addition of risperidone to mood stabilizers in treatment of the manic phase of bipolar disorder over twelve weeks.
METHOD: Patients with manic episodes (n=106) who gave written informed consent were recruited. All subjects were on 1-2 mood stabilizers at the time of initiation of risperidone (range 0.5-4 mg). No other antipsychotic or ongoing benzodiazepine therapy was allowed.
RESULTS: There was a significant decrease in YMRS scores from baseline (27.1 ± 7.5) to week 1 (-10.2, p<0.0001), week 3 (17.3, p<0.0001) and to week 12 (-22.1, p<0.0001). When response was defined as ³50% reduction in YMRS scores from baseline, 30%, 66%, and 88% of patients met criteria at weeks 1, 3, and 12 respectively. Significant decreases in HAM-D 21 scores from baseline (12.3) to week 3 (-5.7, p<0.0001) and week 12 (-5.7, p<0.0001) were also observed . No changes in extrapyramidal symptoms were noted between baseline and endpoint. The mean daily dose of risperidone was 2 mg with a median of 1.8 mg and a range of .4 mg to 4.2 mg.
CONCLUSION: These results suggest the addition of risperidone to mood stabilizers is safe and effective treatment for acute and continuation treatment of mania.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

257E. Long-term risperidone usage for physical assault in an institutionalized developmentally disabled population. *Nancy C. Brahm, MS, R.Ph., BCPP,* H. Dix Christensen, Ph.D., Robert Brown, Ph.D.; University of Oklahoma; DHS/Developmental Disabilities Services Division, Oklahoma City, OK.

Long-term risperidone usage for disruptive behaviors, including assault, was retrospectively evaluated in institutionalized developmentally disabled adults. All persons residing in two state-run facilities who received a trial of risperidone were included. Monthly behavior reports from the Behavior Medicine Committee were reviewed from a baseline of six months prior to initiation to July 2000. Bi-annual DISCUS (Dyskinesia Identification System: Condensed User Scale) assessments were performed to monitor for long-term adverse effects. Retrospective risperidone usage for treatment of physical assault included 28 persons. Demographics included mean age of 37.5 (range 25-56), 23 males/5 females and intellectual functioning of 3 borderline, 14 mild, 1 moderate, 8 severe, and 2 profound. Maximum total daily dosage of risperidone ranged from 2-6 mg with a 5.1 mg mean. Duration of treatment ranged from 5 to 51 months with a 31-month mean. Behavioral suppression was maintained in 12 consumers, 10 significantly worsened from prior treatment, and 6 (one after a 17-month delay) had significant improvement. In the switch-over to risperidone, 5 consumers had a mild increase in behavior, prior to initiation of cross-tapering. In those consumers who had behavioral improvement/ suppression, the behavior remained reasonably constant for the duration of the exposure. If risperidone was discontinued or the dosage markedly decreased without another suppression drug, the physical assault numbers increased. Our finding that risperidone has efficacy in reducing/maintaining baseline rates of physical assault in about 64% (18/28) of the consumers is consistent with previous reports. Furthermore, the effectiveness can be maintained from 30 up to 50 months.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

258E. Risperidone and olanzapine in elderly patients with schizophrenia and schizoaffective disorder. *Dilip V. Jeste, M.D.,* Subramoniam Madhusoodanan, M.D., Yoram Barak, M.D., Rick A. Martinez, M.D., Ramy Mahmoud, M.D., Paul Kershaw, M.D.; University of California, San Diego, San Diego, CA; VA San Diego Healthcare System, San Diego, CA; St. John's

Episcopal Hospital, Far Rockaway, NY; Abarbanel Mental Health Center, Bat-Yam, Israel; Janssen Pharmaceutica Products, L.P., Titusville, NJ.

BACKGROUND and METHODS: In an international, double-blind, 8-week study, 176 patients aged >60 years and with DSM-IV schizophrenia or schizoaffective disorder were randomly assigned to receive flexible doses of risperidone (1-3 mg/day) or olanzapine (5-20 mg/day).
RESULTS: At median doses of 2 mg/day of risperidone and 10 mg/day of olanzapine, PANSS total score (primary endpoint) decreased significantly in both groups at endpoint ($p<0.001$). Between-group differences at endpoint were not significant. Baseline and endpoint scores on Clinical Global Impressions scale were similar in the 2 groups. Two-thirds of all patients had minimal or greater improvement on CGI. Extrapyramidal Symptom Rating Scale (ESRS) scores were equivalent at baseline and improved significantly in risperidone-treated patients at every assessment but showed significant improvement only at week 8 in the olanzapine group. Total EPS-related adverse events were reported in 9% of the risperidone patients and 14% of the olanzapine patients. Risperidone and olanzapine groups did not differ in incidence of common adverse events.
CONCLUSIONS: At doses appropriate in elderly patients with schizophrenia, reductions in psychopathology were seen in both treatment groups with a greater numeric improvement in the risperidone group at every timepoint. Overall side effect profiles were similar, with significant reductions in total ESRS scores in risperidone patients but not olanzapine patients at most timepoints.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

259E. Risperidone in children with various disruptive behavior disorders, subaverage IQ and comorbid ADHD. *Atilla Turgay, M.D.,* Michael G. Aman, Ph.D., Carin Binder, B.Sc.; Scarborough Hospital, Scarborough, ON, Canada; Nisonger Center UAP, Columbus, OH; Janssen-Ortho, Inc., Toronto, ON, Canada.

PURPOSE: Test the hypothesis that risperidone is effective in treating symptoms of ADHD in children with a concomitant diagnosis of ADHD associated with subaverage IQ and conduct disorder, oppositional defiant disorder or disruptive behavior disorder-NOS.
METHODS: 110 children, 5-12 years, IQ 36-84 with various disruptive behavior disorders were randomized in a 6-week, double-blind trial to risperidone or placebo. Comorbid ADHD existed in 84/110 children treated with/without psychostimulants. Psychostimulants were initiated prior to trial entry and maintained at stable doses throughout the trial.
RESULTS: Mean dose of risperidone was 0.033 mg/kg/day (mean daily dose was 0.98 mg). The hyperactivity subscale of the Nisonger Child Behavior Rating Form (NCBRF) and Hyperactivity/Noncompliance subscale of the Aberrant Behavior Checklist both showed a significant decrease in children treated with risperidone. The effect was detected in the risperidone with/without psychostimulant groups when compared to placebo with/without psychostimulants indicating that the efficacy of risperidone is independent from concomitant use of psychostimulants. No unexpected adverse events or laboratory findings were noted in either group.
CONCLUSIONS: Risperidone is effective and safe in reducing symptoms of comorbid ADHD in children with sub-average IQ and various disruptive behavior disorders.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

260E. Pharmacologic management of acute delirium in elderly patients with dementia: a naturalistic, prospective comparison of atypical antipsychotics and haloperidol. *Larry Tune, M.D.,* D. Jewart, Ph.D., S. Egeli, Y. Greene, M.D.; Emory University, Atlanta, GA.

PURPOSE: In an ongoing prospective investigation of elderly demented patients, the efficacy and safety of atypical antipsychotics and haloperidol for the management of delirium were evaluated.
METHODS: All patients satisfied DSM IV criteria for delirium. Patients were evaluated with the Confusion Assessment Method, the MMSE, the Cognitive Test for Delirium, the Simpson Scale for EPS, and the Pittsburgh Agitation Scale.
RESULTS: Among the 52 patients studied to date, 15 received monotherapy with risperidone, 5 with olanzapine, and 7 with quetiapine; 9 received standing doses of haloperidol, 7 PRN haloperidol, and 9 a combination of typical and atypical antipsychotics. Average length of stay (ALOS) was 13.8 days for patients receiving all atypicals, 13.4 days for standing doses of haloperidol, 29.4 days for PRN haloperidol, and 22.3 days for the combination group. EPS ratings improved overall in patients receiving atypicals, while those receiving combination antipsychotics or haloperidol alone showed significant deterioration in EPS.
CONCLUSIONS: These preliminary data show the superiority of atypical antipsychotics to standard therapy with haloperidol, and especially to combination therapy with typical and atypical antipsychotics, for the management of acute delirium in elderly patients with dementia.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

261E. Probenecid effects on the disposition of olanzapine and risperidone. *John S. Markowitz, Pharm.D.,* C. Lindsay DeVane, Pharm.D., Heidi L. Liston, Pharm.D., David W. Boulton, Ph.D., S. Craig Risch, M.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: We compared the effect of probenecid (PB), a known inhibitor of UDP-glucuronosyltransferases (UDPGT) on the disposition of risperidone and olanzapine. It was hypothesized that the disposition of olanzapine, which undergoes extensive glucuronidation would be altered in the presence of probenecid while risperidone disposition would be relatively unaffected.
METHODS: In a single-dose, randomized, four-period, double-blind, crossover study, 12 healthy volunteers, aged 22-42 years, received a single dose of 5 mg of olanzapine or 1 mg of risperidone with and without PB 500 mg (8 doses over 4 days). Multiple blood samples were analyzed to assess the 48-hour time course of risperidone and olanzapine. Urine was assayed for free and glucuronidated drugs.
RESULTS: Significant differences were observed between plasma pharmacokinetic parameters (C_{max} [$p<0.05$)]; AUC_{0-24} [$p<0.01$]; $t1/2\alpha$ [<0.001]) when olanzapine was administered with PB. Clearance and $t_{1/2}\beta$ were not significantly different between the treatment phases. Risperidone pharmacokinetics were not significantly different.
CONCLUSION: Inhibition of UDPGT appeared to influence the disposition of olanzapine but not risperidone. Phase II metabolism may significantly influence the disposition of antipsychotic drugs and may be an important aspect in the variability in metabolism, participation in drug-drug interactions, and clinical response to these agents.
Presented at the 41st Annual Meeting of the New Clinical Drug Evaluation Unit, Phoenix, AZ, May 28-31, 2001.

Pulmonary

262. Characterizing asthmatics with and without premenstrual asthma. *Mary H.H. Ensom, Pharm.D.,* Gina Chong, B.Sc.Pharm. candidate, Bev Beaudin, RRT, Stephen Shalansky, Pharm.D., Tony R. Bai, M.D.; University of British Columbia; St. Paul's Hospital, Vancouver, BC, Canada.

PURPOSE: To identify demographic and clinical factors that may distinguish an asthmatic with premenstrual asthma (PMA) from one without PMA.
METHODS: Twenty-five asthmatic women, with regular menstrual cycles and not on systemic corticosteroids or hormonal contraceptives, completed a one-month evaluation to determine if they had PMA. Following informed consent, subjects completed questionnaires and physical and spirometric exams. They were taught how to use a peak flow meter, and to document daily asthma symptoms (via visual analog scales) and morning and evening peak expiratory flow rates (PEFR) for one entire menstrual cycle. Those women who experienced ≥20% premenstrual worsening of asthma symptoms and/or of PEFR were deemed to have PMA. Statistical parametric and non-parametric analyses were performed, with significance defined as $p\leq0.05$.
RESULTS: Fifteen of 25 subjects (60%) had PMA [based on PEFR (n=11) and symptoms (n=9)]. With the exception of radial pulse and pattern of inhaled short-acting β_2-agonist use, no significant difference was found in any demographic factor between women with and without PMA. Some, but not all, of the factors evaluated are as follows:

Factor	PMA (n=15)	No PMA (n=10)	Factor	PMA (n=15)	No PMA (n=10)
Age (years)	38.0±7.4	39.0±7.7	FEV_1 (L/sec)	2.63±0.64	2.77±0.54
Height (cm)	163.8±6.5	164.4±5.8	FVC (L/sec)	3.72±0.65	4.01±0.43
Weight (kg)	74.6±12.1	69.1±9.6	FEV_1/FVC (%)	72.28±11.46	71.57±9.14
Length of cycle (days)	28.4±0.9	27.7±1.4	Within-cycle variability in symptoms (visual analog scales)		
	132.7±89.9	159.5±119.0			
Radial pulse (min^{-1})	70.5±8.4	58.6±10.2			
Respiratory rate (min^{-1})	12.5±1.0	12.0±0.0	Within-cycle variability in morning PEFR (L/min)		
	147.5±100.7	145.0±113.1			
Short-acting beta$_2$-agonist (daily, >once weekly, >once monthly, <once monthly, nil for 3 months)	3,5,1,2,4	5,1,2,2,0	Within-cycle variability in evening PEFR (L/min)		
	130.5±110.0	162.5±124.1			

CONCLUSIONS: Differences in radial pulse and frequency of β_2-agonist use between asthmatics with PMA versus those without, warrant further study. Interestingly, subjects without PMA had greater within-cycle variability in asthma symptoms and evening PEFR than subjects who met the criterion of ≥20% premenstrual worsening. These preliminary findings may have educational and monitoring implications for female asthmatics.

263. FEV_1 dose response to albuterol metered-dose inhaler (MDI) in patients with asthma: comparative evaluation of administration through an Aerochamber valved holding chamber versus an Easivent valved holding chamber. Dennis M. Williams, Pharm.D., Andrea M. Wessell, Pharm.D., Mary K. Williams, Pharm.D., Tina P. Brock, M.S., Jeanie Mascarella, R.N., James F. Donohue, M.D.; University of North Carolina, Chapel Hill, NC.

PURPOSE: The objective of this study was to compare the bronchodilator response to albuterol when inhaled from a MDI attached to an Aerochamber versus a MDI attached to an Easivent.
METHODS: This double-blind, randomized crossover study was conducted in fifteen subjects with chronic stable asthma. All subjects were ≥ 18 years of age and qualified at screening if they exhibited an FEV_1 response of ≥ 12% to albuterol via MDI (90 to 720 µg).
Participants were randomly assigned to receive albuterol by MDI attached to one of two holding chambers on 2 consecutive days between 5:30 a.m. and 10:00 a.m. Albuterol doses (90 µg, 90 µg, 180 µg, 360 µg) were administered every 20 to 30 minutes. Spirometry was performed at baseline and 20 minutes after each dose. Safety assessments (e.g., blood pressure, heart rate, and respiratory rate) were performed after each dose. The primary outcome measure was FEV_1 achieved on each study day. The percent improvement in FEV_1 at each dosing point was also compared.
RESULTS: A dose response to albuterol was evident with each device. The maximum FEV_1 achieved was not statistically different between the chambers (p=0.886). The mean percent maximum improvement was similar (33% versus 32.5%; p=0.728). There were no significant differences in the percent improvement at each dosing point. The greatest response was with the initial dose of albuterol (~20% improvement over baseline).
CONCLUSIONS: The dose response to inhaled albuterol was not significantly different when inhaled via MDI through an Aerochamber or Easivent valved holding chamber.

264. The effect of volume on *in-vitro* performance characteristics of an MDI spacer fashioned from a plastic cold-drink bottle. Michael J. Asmus, Pharm.D., *Stacy Amburgy, Pharm.D.,* Judy Liang, Pharm.D., Intira Coowanitwong, M.S., Ramin Vafadari, Günther Hochhaus, Ph.D.; Shands HealthCare; University of Florida Gainesville, FL.

PURPOSE: This study documented how volume changes in a spacer fashioned from a plastic bottle affect the in vitro respirable dose of fluticasone from a metered-dose inhaler (MDI).
METHODS: The respirable dose (1-5 µM) of fluticasone aerosol emitted from a Flovent(R) MDI attached to four spacers was determined by using a cascade impactor model (USP-24, 1895-1912). The spacers (237, 500, 1000, and 1500 ml) were fashioned from cold drink containers modified to accept the MDI actuator (Arch Dis Child 2000, 82:490-2). Ten 110-µg puffs were actuated through each spacer into the impactor via USP throat and adapter. Airflow through the impactor was calibrated to 28.3 L/min ± 5%. Fluticasone was washed from individual impactor stages with 50% methanol and quantified via HPLC-UV. Respirable doses from five runs with each spacer were compared to MDI alone using ANOVA with Tukey's multiple comparison test.
RESULTS: Mean (SD) respirable dose per each 110 µg actuation was 46.2 (2.8) µg for MDI alone, 51.6 (1.9) µg for MDI + 237 ml spacer, 42.4 (7.0) µg for MDI + 500 ml spacer, 42.2 (6.5) µg for MDI + 1000 ml spacer and 39.5 (6.7) µg for MDI + 1500 ml spacer. Only the difference between the smallest and largest spacers were significant (p<0.05).
CONCLUSION: The volume of a spacer fashioned from a cold drink bottle has no effect on the respirable dose of fluticasone from a MDI. None of the spacers tested altered the respirable dose of fluticasone compared to the MDI alone.

Substance Abuse/Toxicology

265. A randomized controlled trial comparing intensive and non-intensive smoking cessation interventions provided by community pharmacists. *Rachel L. Couchenour, Pharm.D., BCPS, CDE,* Russell Goodman, Ph.D. candidate, Deborah S. Carson, Pharm.D., BCPS, Rachel Calimlim, Pharm.D. candidate; Medical University of South Carolina, Charleston, SC.

PURPOSE: To evaluate smoking cessation rates of a structured intensive community-pharmacy based intervention compared to a non-intensive intervention.
METHODS: A randomized controlled study of 167 participants enrolled by 17 community pharmacists. The intensive smoking cessation intervention consisted of nine visits with a pharmacist whereas the non-intensive intervention consisted of two visits. The primary outcome was self-reported smoking cessation at six months.
RESULTS: At baseline, the intensive and non-intensive groups were statistically similar with respect to mean age (47.0 ± 9.3 and 45.6 ± 11.2 respectively), gender distribution, and ethnicity. However, participants in the intensive group smoked more cigarettes on average than those in the non-intensive group (26.1 ± 12.7 vs 21.3 ± 12.7 p=0.02). The mean number of previous quit attempts was 2.9 ± 2.5 and 2.9 ± 3.0 in the intensive and non-intensive groups, respectively (p=NS). Twenty of 87 and 49 of 78 participants in the intensive and non-intensive groups respectively completed their 6-month study visit. Of the completers, 14 intensive (70%) and 15 non-intensive (30.6%) group members were smoke-free (p=0.0026). However, if all participants who did not complete their final visit are considered to be smokers, the proportion of smoke-free individuals is virtually identical in the two groups. Of the completers who abstained 'some' but were not smoke free at 6-months, the mean number of days abstinent was significantly greater in the intensive group, (77 ± 27 vs 22 ± 20.1, p=0.01).
CONCLUSION: This intensive intervention provided by community pharmacists can be an effective method of helping people quit smoking.

Transplantation/Immunology

266. The cytokine profile elicited by hepatitis A immunization. *Mary S. Hayney, Pharm.D.,* Jessica A. Buck, B.S., Daniel Muller, M.D., Ph.D.; University of Wisconsin, Madison, WI.

PURPOSE: The hepatitis A vaccine is very effective, inducing protective immunity in virtually all vaccinated individuals. Therefore, the immune response to this vaccine is of interest, particularly the cytokine profile. A vigorous interferon γ (IFNγ) response occurs during acute hepatitis A infection followed by high antibody production upon recovery. The purpose of our investigation was to characterize the cytokine profile following hepatitis A immunization using Th1 [IFNγ] and Th2 [interleukin-10 (IL-10)] cytokines.
METHODS: Twenty-one hepatitis A seronegative individuals were immunized with hepatitis A vaccine. Serial blood draws were done on days 0, 2, 5, 7, 10, and 28. Peripheral blood mononuclear cells (PBMC) were cultured with hepatitis A virus for 96 hours. The supernatants were harvested and IFNγ and IL-10 concentrations were measured by ELISA (OptEIA, BD Biosciences). ANOVA was used to detect differences in cytokine production over baseline.
RESULTS: Significant amounts of IFNγ (p<0.0005) and IL-10 (p=0.02) were produced by antigen specific stimulation of PBMC. The peak production for both cytokines is on day 7 (p<0.05 for both IFNγ and IL-10)
CONCLUSIONS: An antigen specific cytokine response follows hepatitis A immunization. The cytokine response parallels that following natural infection.

267. The relationship of P-glycoprotein genotypes and cyclosporine pharmacokinetic parameters among healthy volunteers. *David I. Min, Pharm.D., FCCP,* Vicki L. Ellingrod, Pharm.D., BCPP, Craig Herman, Pharm.D. candidate; University of Iowa, Iowa City, IA.

Cyclosporine (CsA) is a substrate for P-glycoprotein (P-gp) and its pharmacokinetics is predicted by intestinal P-gp expression. Recently alterations in the human multi-drug resistance (MDR-1) gene have been found to correlate with the C3435T polymorphism of P-gp. Individuals homozygous for this polymorph have significantly lower MDR-1 expression and higher plasma concentrations of P-gp substrates such as digoxin.
PURPOSE: To determine the relationship between P-gp genotypes and its substrate, CsA pharmacokinetic parameters among healthy volunteers.
METHODS: The oral CsA pharmacokinetic study was performed in 14 healthy subjects. Blood cyclosporine concentrations were measured by high performance liquid chromatography. Concentration versus time data were analyzed by non-compartmental method using WinNonLin, and the blood samples were genotyped for the C3435T polymorphism of P-gp using the polymerase chain reaction and a restriction digest according to Hoffmeyer's method. Each CsA pharmacokinetic parameters were compared using Mann-Whitney test according to his or her P-gp genotypes.
RESULTS: There were seven (7) homozygous C/C, six (6) C/T and one (1) homozygous T/T genotypes in these 14 healthy volunteers. According to their genotypes, mean Tmax 1.6 ± 0.3 hr, mean Cmax 1337 ± 329 ng/ml, mean CL/F 66.5 ± 18.3 L/hr, and mean AUC 5642 ± 1577 ng.hr/ml in C/C group and mean Tmax 2.0 ± 0.6 hr, mean Cmax 1540 ± 721 ng/ml, mean CL/F 55.2 ± 18.9 L/hr, and mean AUC 6902 ± 1405 ng.hr/ml in C/T+T/T group and none of these parameter comparisons were statistically significant.
CONCLUSIONS: There were no statistical difference in CsA pharmacokinetics among different P-gp genotypes in these 14 healthy subjects. Further study with larger sample size may be needed to confirm these results.

268. Assessment of statin therapy guidelines in cardiac transplant patients. *Abdulrazaq S. Al-Jazairi, Pharm.D.,* Evan Loh, M.D., Daniel J. Rader, M.D., Susan C. Brozena, M.D., Lee Goldberg, M.D., Mariell J. Jessup, M.D., Brian Drachman, Eric J. Stanek, Pharm.D., Sarah A. Spinler, Pharm.D., FCCP; Philadelphia College of Pharmacy; University of Pennsylvania, Philadelphia, PA

PURPOSE: Statin therapy has been associated with a reduction in the incidence of coronary artery vasculopathy (CAV), rejection and mortality in heart transplant (OHT) patients. The relationship between the observed benefits of statins and the reduction in LDL cholesterol is controversial and the NCEP has no guidelines addressing OHT hyperlipidemia treatment. Therefore, a consensus guideline was developed at our hospital in 1998 outlining statin administration guidelines for OHT recipients. Our guidelines recommend initiating statins for total cholesterol (TC) >200 mg/dl and/or LDL >100 mg/dl. This study assessed guideline compliance and the relationship between statin therapy, lipoprotein levels, CAV and achievement of NCEP II LDL target.

METHODS: Outpatient medical charts from all living adult OHT recipients (n=328; mean time since OHT 4.74 ± 3.40 years) who presented to OHT clinic between July 1999 to June 2000 were reviewed. Descriptive and appropriate parametric and nonparametric statistical analyses were performed using SAS ver. 6.12 with p values of ≤0.05 considered statistically significant.
RESULTS: 192/328 patients (59%) had LDL levels <100 mg/dl with 237 patients (72%) prescribed a statin (1.7 ± 1.1 years). Atorvastatin (63%) and pravastatin (27%) were the most frequently prescribed statins. 7.0% were prescribed other lipid-lowering therapies, including 3% prescribed a combination regimen. Patients prescribed a statin had lower TC (185 ± 40 vs 202 ± 55, p=0.001), LDL (95 ± 29 vs 108 ± 36, p=0.0006), and were more likely to meet NCEP II LDL target (81% vs 63%, p=0.0003) compared to patients not prescribed statins. LDL < 100 mg/dl was observed more frequently in patients with CAV compared to those without CAV (69% vs 55%, p=0.03). Possible statin adverse effects (primarily muscle pain) were reported in 22.7% (3 cases myopathy), resulting in discontinuation in 2.7%.
CONCLUSIONS: At our hospital, nearly three-quarters of OHT recipients received a statin. While more than 80% met the NCEP II LDL target, only 58% met our institutional target of LDL <100 mg/dl. Few patients discontinued statin therapy. Additional efforts are needed to enhance compliance with the guidelines.

269. Basiliximab provides no pharmacoeconomic benefit for induction therapy in living-related renal transplants. *Jason A. Crompton, Pharm.D.,* Troy Somerville, Pharm.D., Tami Quinn, Edward Nelson, M.D., John Holman, M.D., Fuad Shihab, M.D.; University of Utah Hospitals and Clinics, Salt Lake City, UT.

PURPOSE: Few studies have reported pharmacoeconomic data with basiliximab (BAS). We report our experience with BAS vs no induction (CNV) in adult living-related donor renal transplant recipients (LRD) focusing on economic benefit.
METHODS: Between 1/99 and 6/00, 27 living-related renal transplants were performed using quadruple immunosuppression with BAS, cyclosporine microemulsion, azathioprine, and prednisone. An equal comparison group of living-related renal transplants that received triple immunosuppression (CSA, AZA, P) between 6/97-6/99 were used for comparison.
RESULTS: Surprisingly, the incidence of AR was 22% (6/26) in the BAS group and 19% (5/26) in the CNV group. Renal function, as measured by average serum creatinine, was similar at months 1, 2, 3, 6, and 12 for both groups. 1-year graft survival was 85% (22/26) in the BAS group vs 100% in the CNV group. Incidence of infectious complications was similar in both groups. No adverse effects were reported with administration of basiliximab. Mean initial hospitalization charges were $66,349 vs $52,081 in the BAS and CNV groups, respectively. The CNV group had an increased number of readmissions (18 vs 14 in the BAS group), but the average charge per readmission was greater for the BAS group ($21,610 vs $10,240 in the CNV group). All money figures have been converted to 2000 US dollars.
CONCLUSION: BAS did not provide a clear clinical efficacy benefit or prove to be cost-effective when compared to the use of no induction in LRD recipients.

270E. Olestra decreases cyclosporine absorption and total exposure that is not reflected by trough concentrations. *K. Troy Somerville, Pharm.D.,* Cynthia J. Terrill, Jennifer Lill, Pharm.D., Joseph R. Sherbotie, M.D.; University of Utah, Salt Lake City, UT; University of Washington, Seattle, WA.

BACKGROUND: Olestra (Olean®) is a palatable, non-absorbable, non-toxic fat substitute found in many snack foods. Olestra decreased the absorption of fat-soluble vitamins and potentially could decrease the absorption of fat-soluble medications including cyclosporine (CsA).
METHODS: We conducted a prospective, open-label, crossover pharmacokinetic trial assessing the effect of olestra on CsA. All patients participated in two study periods: 1) Patients were given their normal dose of Neoral(R) without olestra. 2) Patients were given their usual dose of Neoral combined with 0.35 g/kg (maximum 16 grams of olestra or approximately 2 ounces of "WOW" potato chips). The two study periods were separated by a minimum 7-day washout period. CsA blood concentrations (Abbott TDX Immunoassay Methodology) were obtained at 1, 2, 3, 4, 6, 8 and 12 hours after drug administration to calculate pharmacokinetic parameters (AUC, Cmax, oral clearance, and half-life). Concomitant medications know to interact with CsA could not be used by patients in the study.
RESULTS: The study included 7 patients (71% male) with an average age of 15.3 (range 9 to 18) years. Time from transplant ranged from 5 to 24 months.

Parameter	Neoral Alone	Neoral + Olestra	p value
Mean CsA AUC (ng•hr/ml)	5018	4086	<0.001
CsA Cmax (ng/ml)	1202	876	0.015
CsA Oral Clearance (ml/min)	431	531	<0.001
CsA Half-life (hr)	4.767	4.771	NS
CsA Trough (ng/ml)	143	124	NS

Our patients demonstrated significantly lower CsA AUC with olestra despite no significant change in trough levels.
CONCLUSION: Olestra decreases total CsA decreases total CsA exposure in pediatric renal transplant recipients. The noted decrease in AUC was not adequately predicted by CsA trough values which could lead to rejection episodes in the clinical setting.
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271E. FTY720 combined with Neoral® and corticosteroids is effective and safe in prevention of acute rejection in renal allograft recipients (3-month data). *Janet L. Karlix, Pharm.D.,* Helio Tedesco, M.D., Barry D. Kahan, M.D., Ph.D., Georges Mourad, M.D., Yves V.Z. Vanrenterghem, M.D., Josep Grinyo, M.D., W. Weimar, M.D., Pascale Pellet, Ph.D., Lawrence Chodoff, Pharm.D., Tomasz Sablinski, M.D., Ph.D.; University of FL, Gainesville, FL; Hospital do Rim e da Hipertensao, Sao Paulo, Brazil; University of Texas, Houston, TX; Gasthuisberg, Belgium; Hospital Ciudad, Sanitaria de Bellvitge, Barcelona, Spain; Academisch Ziekenhuis, Rotterdam, Netherlands; Novartis Pharmaceuticals, Basel, Switzerland; Novartis Pharmaceuticals, Summit, NJ.

FTY720 is a potent immunomodulator with unique effects on lymphocyte homing.
METHODS: Multicenter, randomized, open-label dose finding study to evaluate safety, tolerability and preliminary efficacy of FTY720 vs mycophenolate mofetil (MMF) with Neoral® (cyclosporine, USP [Modified]) and corticosteroids (CS) in de novo renal transplantation. Adults aged 18-65 undergoing primary cadaver or living donor (non-HLA identical) renal transplantation, who exhibited good allograft function during the first 12 hours post-transplant, were randomized to one of four regimens of FTY720 (loading dose [LD] on Day 1, followed by a once daily maintenance dose), or to MMF 2 g/day. All patients received concurrent Neoral + CS per center standard. Induction with antilymphocyte antibodies (Ab) or anti-IL-2Rα Ab was not allowed.
RESULTS: 209 patients were enrolled, and efficacy data are available for all patients at 3 months. The incidence (%) of biopsy-confirmed acute rejection in the different treatment groups was FTY720 1 mg LD + 0.25 mg QD: 10/43 (23.3%), FTY720 2 mg LD + 0.5 mg QD: 15/43 (34.9%), FTY720 4 mg LD + 1.0 mg QD: 7/40 (17.5%), FTY720 4 mg LD + 2.5 mg QD: 4/41 (9.8%), vs MMF 2 g/day: 7/41 (17.1%).
SAFETY: FTY720 was well tolerated. Overall incidence of serious adverse events or infections of any type was comparable in MMF and FTY720 treated patients. Episodes of transient bradycardia without sequelae, most of which occurred within first 24h post-transplant, were reported more frequently in FTY720-treated patients (12%) vs MMF-treated patients (4.9%). Graft survival is 97.6% (2, 1 and 2 graft losses in FTY720 0.25 and 1.0 mg maintenance dose groups and MMF group, respectively) and patient survival is 99.5% (1 death in FTY720 2.5 mg maintenance dose group).
CONCLUSIONS: FTY720 appears to be effective in the prevention of acute rejection in de novo renal transplant patients when used with Neoral and CS. Additional trials are underway to evaluate the role of FTY720 in the prevention of acute rejection and graft loss after renal transplantation.
Presented at the Joint Annual Meeting of the American Society of Transplantation and the American Society of Transplant Surgeons, Chicago, IL, May 14, 2001.

272E. Safety and pharmacodynamics of multiple doses of FTY720 in stable renal transplant recipients. *Janet L. Karlix, Pharm.D.,* Barry D. Kahan, M.D., Ph.D., Lawrence Chodoff, Pharm.D., Alan B. Leichtman, M.D., Ronald Ferguson, M.D., Ph.D., Shamkant Mulgaonkar, M.D., Tomas A. Gonwa, M.D., Jennifer Dehlinger, R.N., Robert L. Schmouder, M.D., Milbohr D'Silva, Tomasz Sablinski, M.D., Ph.D.; University of Florida, Gainesville, FL; University of Texas, Houston, TX; Novartis Pharmaceuticals, Summit, NJ; University of Michigan Medical Center, Ann Arbor, MI; Ohio State University, Columbus, OH; Saint Barnabas Medical Center, Livingston, NJ; Baylor University Medical Center, Dallas, TX; Novartis Pharmaceuticals, Horsham, United Kingdom.

PURPOSE: FTY720 is a novel immunomodulator which selectively alters lymphocyte homing in peripheral blood and has shown synergy in prolongation of allograft survival in preclinical models. We present results of a multicenter, randomized, double blind, placebo-controlled, ascending-dose study.
METHODS: Adults at least one year post-renal transplant, maintained on Neoral® (cyclosporine, USP [Modified])+ steroids were randomized to receive FTY720 0.125, 0.25, 0.5, 1.0, 2.5, 5.0 mg or placebo once daily for 28 days and then monitored for an additional 28 days.
RESULTS: 76 patients were enrolled (FTY720 61, placebo 15). Study medication was well tolerated without major safety concerns. Six serious adverse events were reported in FTY720-treated patients, 4 of which were suspected to be related to study medication, and all resolved with conservative management. Infections occurred in 17/61 (28%) FTY720-treated patients vs 5/15 (33%) placebo patients. There were no clinically relevant differences between treatments in labs, vital signs, ECG, exercise oximetry or pulmonary functions.
Pharmacodynamics: peripheral blood lymphocyte (PBL) reduction was noted 2 hours after the first dose; nadir PBL count at 25-30% of baseline occurred on day 1 within 8 hours after FTY720 2.5 mg or 5.0 mg. FTY720 doses ≥1.0 mg/day maintained PBL at 15-30% of baseline for up to 28 days. Recovery was

evident within 2 days after the last dose with a trend toward complete recovery in all dose groups at end of study (day 56). All lymphocyte subsets measured were equally affected.
CONCLUSIONS: FTY720 in doses up to 5.0 mg/day for 28 days was well tolerated in stable renal transplant patients maintained on cyclosporine and steroids. FTY720 resulted in a significant, reversible decrease in PBL, the duration and intensity of which appear to be dose dependent.
Presented at the Joint Annual Meeting of the American Society of Transplantation and the American Society of Transplant Surgeons, Chicago, IL, May 14, 2001.

273. Pharmaceutical care services enhance transplant patients adherence to immunosuppressive therapy. *Marie A. Chisholm, Pharm.D.,* Bridgett D. Kendrick, C.Ph.T., Charlene Garrett, Diane Glenn, Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This randomized, controlled trial analyzes the impact of pharmaceutical care services on renal transplant patients' adherence with immunosuppressive (IS) agents.
METHODS: Patients who received a renal transplant at the Medical College of Georgia during a 2-year period were randomized in the intervention or control group. In addition to routine clinic services at each clinic visit, patients in the intervention group received clinical pharmacy services which included medication histories and review of patients' medications with an emphasis on optimizing and improving patients' adherence to medication therapy to achieve desired outcomes and minimize adverse medication events. Patients in the control group received the same routine clinic services as the intervention group except that they did not have any clinical pharmacist interaction. Adherence rate (AR) was calculated by using refill records and medical chart data and patient's adherence status was determined from the AR. The AR, the fraction of patients remaining adherent, and the mean time patients were adherent were compared between groups. Adherence odds ratio was calculated. Whether there was a difference in the frequency of patients achieving "target" immunosuppressive levels in the control and study groups were also evaluated.
RESULTS: The mean AR for patients who had clinical pharmacist intervention (n=12) was statistically higher then the control group's (n=12) mean AR ($p<0.001$). Patients in the intervention group had a longer duration of adherence ($p<0.05$), had six times the odds of adhering with IS therapy, and had a greater achievement of "target" levels ($p<0.05$) than patients in the control group.
CONCLUSIONS: Patients who received pharmaceutical care services with traditional patient care services had better adherence with immunosuppressants than patients who only received traditional patient care services.

274. Once weekly fluconazole (Flu) prophylaxis in kidney transplant patients (KTP). *Emiko Bolton, Pharm.D.,* Ivy Lee, Pharm.D., BCPS, B. Joseph Guglielmo, Pharm.D., Stephen Tomlanovich, M.D.; University of California, San Francisco, CA.

PURPOSE: Fungal infection is associated with significant morbidity and mortality in the solid organ transplant population. One approach to decrease the risk of systemic infection has been primary antifungal prophylaxis. This study compared the efficacy of prophylactic clotrimazole to once-weekly FLU in KTP.
METHODS: The study was a retrospective review of KTP receiving transplants during 1994 (control patients) and 1997-1998 (study patients). Control patients received clotrimazole troches 10 mg four times a day while study patients received fluconazole 100 mg once weekly. Prophylaxis was continued for 1 month after kidney transplantation in both groups. Systemic, deep-seated fungal infection was defined as a positive fungal culture from blood, normally sterile tissue or body fluids, excluding urine, stool, and sputum. The incidence of deep-seated infection in clotrimazole and Flu-treated patients was evaluated.
RESULTS: A total of 597 kidney transplant recipients were reviewed. Twelve out of 216 (5.6%) of patients receiving clotrimazole had microbiologically documented deep-seated fungal cultures. In contrast, only 8/381 (2.0%) of Flu-treated patients had confirmed deep-seated infection ($p<0.025$). The incidence of deep-seated infection specifically due to *Candida albicans* was significantly greater in 1994 (7/216 (3.2%)) when compared to 1997 and 1998 (1/381 (0.3%); $p<0.01$). No microbiologically documented fungemia was documented in the Flu group; one fungemia was noted in clotrimazole-treated patients.
CONCLUSION: A novel dose of prophylactic fluconazole 100 mg once weekly after kidney transplant is more effective than clotrimazole administered four times a day with the primary benefit a reduction in the incidence of infection due to *Candida albicans*.

275. Pharmacokinetics and protein binding of mycophenolic acid in stable lung transplant recipients. *Mary H.H. Ensom, Pharm.D.,* Nilufar Partovi, Pharm.D., Diane Decarie, B.Sc., Randall J. Dumont, M.Sc., Guy Fradet, M.D., Robert D. Levy, M.D.; University of British Columbia, Vancouver, BC, Canada.

PURPOSE: The purpose of this study was to characterize the pharmacokinetic profile and protein binding of mycophenolic acid (MPA) in stable lung transplant recipients.
METHODS: Seven patients were entered into this open-label study. Upon administration of a steady-state morning mycophenolate mofetil (MMF) dose, blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 9, 10, and 12 hours post-dose. Total MPA concentrations were measured by a validated HPLC method with ultraviolet detection and followed by ultrafiltration of pooled samples for free MPA concentrations. Area under the curve (AUC), peak concentration (Cmax), time to peak concentration (Tmax), trough concentration (Cmin), free fraction (f), and free MPA AUC were calculated by traditional pharmacokinetic methods.
RESULTS: Patient characteristics included: 3 males and 4 females, an average of 4.4 years post-lung transplant (range: 0.3-11.5 year), mean (± SD) age of 50 ± 10 year and weight 69 ± 20 kg. Mean albumin concentration was 3.7 ± 0.3 g/dl and serum creatinine was 1.6 ± 0.6 mg%. All patients were on cyclosporine and prednisone. MMF dosage ranged from 1 to 3 grams daily (35.5 ± 14.1 mg/kg/day; range 15.2-60.0 mg/kg/day). Mean AUC was 45.78 ± 18.35 µg•h/ml (range 16.56-74.22 µg•h/ml), Cmax 17.37 ± 7.69 µg/ml (range 4.92-26.63 µg/ml), Tmax 1.2 ± 0.4 h (range 1.0-2.0 h), Cmin was 3.12 ± 1.41 µg/ml (range 1.47-4.82 µg/ml), f was 2.90 ± 0.56% (range 2.00-3.40%), and free MPA AUC was 1.29 ± 0.50 µg•h/ml (range 0.54-1.88 µg•h/ml).
CONCLUSIONS: This is the first study to determine these pharmacokinetic characteristics of MPA in the lung transplant population. The MPA free fraction in these patients appears to be similar to the average 2 to 3% found in healthy adult individuals, stable renal transplant recipients, and heart transplant recipients. Further studies should focus on identification of MMF dosing strategies that optimize immunosuppressive efficacy and minimize toxicity in lung allograft recipients.

276. The pharmacokinetic effects of sildenafil (Viagra®) on tacrolimus (Prograf®) blood concentrations. *James J. Garnick, Pharm.D.,* Iman Bajjoka, Pharm.D., Viken Douzdjian, M.D., Warren Kupin, M.D., Marwan Abouljoud, M.D.; University of Michigan Health System, Ann Arbor, MI; Henry Ford Hospital, Detroit, MI.

PURPOSE: Tacrolimus (FK-506) is metabolized through the CYP450-3A4 enzyme pathway. Sildenafil, used for erectile dysfunction, is also metabolized through the 3A4 system and is a weak inhibitor of this pathway. FK506 whole blood trough and area-under-the-curve concentrations (AUC) were measured in patients on stable FK506 doses to determine if any changes occurred due to sildenafil administration.
METHODS: Five transplant recipients (2 kidney and 3 liver, 4 African-American and 1 Caucasian) were enrolled in this prospective analysis. The average FK506 dose was 0.06 mg/kg. The study was performed over three consecutive days. On the first day of the study, an FK506 whole blood trough concentration and a 4 hour AUC profile were measured predose and at times 1, 2, 3 and 4 h post dose. Subjects then took a 50-mg dose of sildenafil. On the following day, another trough concentration and 4 hour AUC were performed, starting at 24 hours post the original dose of FK506. On the third day, only a trough concentration was measured, 48 hours post the original dose of FK506.
RESULTS:

	Day 1		Day 2		Day 3
SUBJECT	AUC	C_{min}	AUC	C_{min}	C_{min}
1	18.73	3.8	28.66	2.8	7.8
2	93.43	12.8	106.9	10.8	11.5
3	28.59	6.5	31.3	7.0	6.3
4	93.01	10.0	141.0	7.2	6.3
5	85.3	6.4	168	14.7	20.5

The results comparing pre to post dose AUCs showed an increase in all subjects ($p=0.1$). Some subjects showed an increase in their C_{min}. Subjects 1 and 5 had an increase in C_{min} of 105% and 220%, respectively.
CONCLUSION: The concomitant administration of FK506 and sildenafil is associated with elevated FK506 concentrations. More frequent monitoring of FK506 concentrations is prudent. Clinicians should be aware of this potential drug interaction and be prepared to adjust FK506 therapy on an individual case basis depending on observed concentrations.

277. A clinically significant drug interaction between basiliximab and tacrolimus in renal transplant recipients. *Nicole M. Sifontis, Pharm.D.,* Enrico Benedetti, M.D., Eva M. Vasquez, Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: A recent report of a drug interaction between cyclosporine and basiliximab (BASI) prompted us to investigate whether a similar interaction would occur between tacrolimus (TAC) and BASI. Therefore, the purpose of this study was to evaluate the effect of BASI induction therapy on TAC blood trough concentrations in renal transplant recipients (RTR).
METHODS: 12 adult RTR receiving BASI therapy (20 mg on the day of transplant (Tx) and on day 4 following Tx) in conjunction with TAC-based therapy were included in this analysis. Patients receiving induction therapy with antithymocyte globulin served as the control group (n=8). We compared TAC blood trough levels and TAC dose requirements between the two groups on days 1, 3, 5, 7, 10, 30 and 60 following Tx.

RESULTS: A total of 20 adult RTR (mean age 45.8 ± 11 years) were evaluated. We observed a 63% increase in TAC blood trough concentrations in BASI-treated patients on day 3 compared to controls (p>0.05). Fifty percent of the BASI-treated patients had supratherapeutic TAC blood trough levels (>20 ng/ml, IMX) on day 3 which were associated with the development of acute tubular necrosis. TAC doses were adjusted or withheld (1-3 doses) in patients with supratherapeutic levels hence, TAC trough blood levels on day 5, 7 and 10 were similar between the two groups. The mean dose of TAC during the first week following Tx was significantly lower in the BASI group (0.16 mg/kg/day) vs the control group (0.25 mg/kg/day, p<0.05). By day 30 post-Tx TAC levels trended downward in the BASI group despite similar dose requirements to those observed on day 10 post-Tx. Levels remained stable between 30 and 60 days post-Tx in both groups. TAC dose requirements were lower in the BASI group compared to the control group throughout the entire study period.
CONCLUSION: Our data suggest that a clinically significant drug interaction may occur between BASI and TAC. Diligent TAC monitoring and dose titrations in the early post-Tx period are warranted in patients receiving BASI therapy to minimize the risk of drug toxicity. Similarly, TAC trough levels should be closely monitored during the first month post-Tx to avoid precipitation of an early acute rejection episode.

Urology

278E. Vardenafil, a new selective PDE5 inhibitor, significantly improved all IIEF domains and showed a favorable safety profile in patients with erectile dysfunction (ED) over 12 weeks. *Jay Young, M.D.,* Stephen Auerbach, M.D., Hartmut Porst, M.D.; South Coast Urological Medical Group, Laguna Hills, CA; California Professional Research, Newport Beach, CA; Hamburg, Germany.

PURPOSE: A recent phase II study demonstrated significant improvement in erectile function for patients with ED over placebo for three doses of vardenafil. This report further evaluates the changes in efficacy and adverse event profiles that occurred over time.
METHODS: In a double-blinded, randomized, placebo-controlled, at-home study, 601 men with ED were randomized to take oral doses of placebo or 5 mg, 10 mg, or 20 mg of vardenafil. Efficacy was measured by the International Index of Erectile Function (IIEF) at 4, 8 and 12 weeks. Rates of adverse events (AE) in these 4-week intervals were also calculated.
RESULTS: Mean baseline scores for erectile function ranged from 13.8 to 14.2. By 4 weeks, placebo mean score increased to 15.9 while scores for 5 mg, 10 mg and 20 mg increased to 20.3, 21.5, 23.2 (p<0.001). This improvement was maintained for the 12-week period. Improvement after 4 weeks of treatment was noted for all domains of Orgasmic Function, Intercourse Satisfaction and Overall Satisfaction and a small increase in Sexual Desire. The maximum effect was reached at the highest doses by 4 weeks with a sustained effect throughout the 12 weeks of the study. The most common AEs were headache, flushing and dyspepsia. AEs were either highest in the first 4 weeks or were stable throughout the 12 weeks. No drug-related serious adverse event occurred. This study indicated that vardenafil was well tolerated and may provide both an early and sustained benefit for patients with erectile dysfunction.
Presented at the Annual Meeting of the American Urological Association, Anaheim, CA, June 2-7, 2001.

279E. Vardenafil demonstrates improved erectile function in diabetic men with erectile dysfunction. *Irwin Goldstein, M.D.*; Boston University Medical Center, Boston, MA.

PURPOSE: Patients with diabetes have a higher incidence of erectile dysfunction (ED), but have been shown to be less responsive to available oral ED therapies. A multicenter, randomized, double-blind, placebo-controlled phase III trial has determined the efficacy, safety and tolerability of vardenafil, a new oral agent, in patients with diabetes mellitus and erectile dysfunction.
METHODS: Type 1 (n=54) or 2 (n=398) diabetes mellitus patients with erectile dysfunction lasting >6 months were randomized to take placebo, 10 mg or 20 mg of vardenafil, as needed. Patients were evaluated after a 4-week baseline period and at the end of 12 weeks. Primary efficacy variables were the erectile function domain of the IIEF (IIEF-EF) and the per patient success rates both for vaginal penetration and maintaining erections to complete intercourse by event diary. Responder rates for improved erection were derived from the Global Assessment Question (GAQ).
RESULTS: For the GAQ, the responder rates were 72% and 57% for 20 mg and 10 mg, respectively, in contrast to 13% for placebo. For the IIEF-EF, the final scores for the 20 mg and 10 mg dose were 19.0 and 17.1 compared to 12.6 for placebo. Both the penetration and maintenance diary questions had better responses than placebo for both vardenafil doses. For all variables improvement for vardenafil patients compared to placebo patients was significant (p<0.01). Adverse events were generally mild or moderate.
CONCLUSION: Vardenafil was highly effective in improving erectile function and was well tolerated in diabetic patients with ED.
Presented as the 61st Scientific Sessions of the American Diabetes Association, Philadelphia, PA, June 22-26, 2001.

Women's Health

280. Correlation of cord to maternal ampicillin concentration ratio to time and body mass index. *Patty Fan-Havard, Pharm.D.,* Craig A Pedersen, Ph.D., Jennifer L. Lew, M.D., Jeffrey R. Johnson, M.D., David F. Colombo, M.D.; Ohio State College of Medicine and Public Health, Columbus, OH.

PURPOSE: Intrapartum chemoprophylaxis with penicillin or ampicillin (AMP) is now recommended to prevent vertical transmission of GBS and to reduce the incidence of GBS in newborns. However, data are limited on the achievable concentrations of AMP in the fetus. We investigated the cord serum concentration of AMP obtained at delivery and evaluated the relation of cord-to-maternal AMP concentration ratio compared to time and body mass index (BMI).
METHODS: All subjects received 2 g AMP by IV bolus injection following informed consent. Simultaneous maternal and cord blood samples were obtained at the time of delivery. AMP concentrations were determined by HPLC. Ordinary Least Squares Regression was used to assess the relationship of cord-to maternal ampicillin concentration ratio to time or BMI.
RESULTS: The mean age and the BMI of the 21 subjects were 28 ± 5.2 years and 33.0 ± 7.2 kg/m^2, respectively. The time interval between AMP administration and delivery varied between 0.45 and 5.6 hr. The mean maternal and cord AMP concentrations were 21.2 ± 13.4 µg/ml and 16.0 ± 6.7 µg/ml, respectively. The concentrations of AMP achieved in the cord blood exceed the minimum bactericidal concentration (0.25 to 2.0 µg/ml) by 8- to 64-fold against GBS. A significant positive linear relationship was observed between the ratio of cord-to-maternal AMP concentration and time (Pearson correlation coefficient = 0.569; F (1.19) = 9.09, p=0.0007), but not to BMI.
CONCLUSION: High concentrations of AMP in the cord blood are rapidly achieved. The increase in the ratio of cord-to maternal AMP concentration with time suggests a difference in the clearance of AMP between the mother and the fetus.

281. Knowledge and attitude toward hormone replacement therapy usage in postmenopausal women in Taipei. *Chia-Feng Lai, R.Ph.,* Yue Rong Chen, M.D., She-Yi Wei, B.S., Tsung-Chi Lien, B.S., Hsiang-Yin Chen, Pharm.D.; Taipei Municipal Wan-Fang Hospital; Taipei Medical University, Taipei, Taiwan.

PURPOSE: Compliance to hormone replacement therapy (HRT) is strongly associated to women's knowledge and attitude. For greater understanding the concerns of HRT, the survey was designed to determine the knowledge and attitude toward HRT usage in postmenopausal women in Taipei.
METHOD: Postmenopausal women filled an HRT prescription from the outpatient pharmacy at the Taipei Municipal Wan-Fang Hospital (TMWFH) were invited to fill a questionnaire individually. The questionnaire included 10 questions regards to attitude and 12 for knowledge. Attitude questions were originally developed by Kristi Ferguson and modified by Hazel Sinclair and Patricia Kaufert. Range of attitude score was from 0 to 70, with seven-point scale for each question. Perfect score of knowledge questions was 16, including 12 from risk/benefit and 4 from usage.
RESULTS: Five hundred and twelve postmenopausal women were enrolled in July 2000. Mean knowledge score was 7.36 ± 3.86, including 2.10 ± 1.26 for risk/benefit and 5.30 ± 3.03 for HRT usage. The correct rate of the risk/benefit and usage of HRT were 44.2% and 52.5%, respectively. Attitudes toward HRT and menopause favor neutral or positive direction, with sum of score 43.64 ± 3.83 and average score 4.37 ± 0.43.
CONCLUSION: Results from the survey clearly demonstrated that education on HRT is needed in Taiwan. Confirming women's knowledge of HRT and attitudes about menopausal health may offer opportunities to assist women's decision making about HRT and to improve compliance.

282. Influences of pharmacist-conducted hormone replacement therapy education program on knowledge and attitude in postmenopausal women in Taipei. *Hsiang-Yin Chen, Pharm.D.,* Chia-Feng Lai, R.Ph., Ming-Hui Liao, B.S., Jia-You Fang, Ph.D., Shing-Mei Hsu-Lee, R.Ph.; Taipei Municipal Wan-Fang Hospital; Taipei Medical University, Taipei, Taiwan.

PURPOSE: The use of hormone replacement therapy (HRT) to reduce the risk of major health disorders in later life is well documented. The ability to clearly and objectively inform the women the possible benefits and risks of HRT is a major challenge to health professionals. Recognizing the significance of pharmacists on medication consultation, the study was designed to compare the changes of women's knowledge and attitudes after HRT education provided by pharmacist.
METHODS: Patient who filled HRT prescriptions from the Outpatient Pharmacy at the Taipei Municipal Wan-Fang Hospital (TMWFH) were invited to join the pharmacist-conducted HRT education program. The subjects were randomly assigned to the control and treatment groups. Only subjects in the treatment group were provided with the education and HRT booklet. A questionnaire included attitudes toward menopause and HRT knowledge was administered on the first interview and 1 month later for both groups.
RESULTS: Total numbers of subjects completed the study were 149 in treatment group and 130 in control group from July 2000 to August 2000. Baseline knowledge scores were 7.87 ± 3.69 and 7.28 ± 4.05 for treatment and

control groups, respectively. (p=0.206) Mean difference of knowledge score was significantly higher in treatment group than that in control group (4.2 ± 3.27 versus 0.7 ± 2.93, p<0.0001). Changes in attitude score after the intervention were insignificantly different between two groups (p=0.072).
CONCLUSIONS: Large improvement in HRT knowledge was seen after the health education. The present study demonstrates that providing women with accurate, up-to-date information and enhancing communication with them remains a good challenge for pharmacists in women's health issue.

283. The effect of pregnancy on the pharmacokinetics of low molecular weight heparin. *Mary H.H. Ensom, Pharm.D.,* Elisa-Marie Babor, B.Sc.Pharm. candidate, Edwina Houlihan, RN, Penny J. Ballem, M.D., Mary D. Stephenson, M.D.; University of British Columbia; Children's & Women's Health Centre of British Columbia, Vancouver, BC, Canada.

PURPOSE: The primary objective of this study was to determine whether differences exist in the pharmacokinetics of low molecular weight heparin (LMWH) before pregnancy and during the first, second, and third trimesters of pregnancy in women with the antiphospholipid antibody syndrome (APS). A secondary objective was to compare pre-pregnancy and postpartum bone mineral density (BMD). To date, no LMWH pharmacokinetic or BMD data exist for women with APS.
METHODS: Following informed consent, 5 patients contemplating pregnancy were taught how to self-inject LMWH (dalteparin) subcutaneously and follow an empiric dosing schedule. They underwent bone densitometry studies (via dual energy x-ray absorptiometry) before and after pregnancy and 4 serial blood sampling days (pre-pregnancy, first trimester, second trimester, and third trimester). Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours following a steady-state dose of LMWH and plasma concentrations measured by determining anti-factor X_a activity using an amidolytic method with chromogenic substrate. Pharmacokinetic parameters were calculated by noncompartmental methods. One-way repeated measures analysis of variance (pharmacokinetic data) and paired t-tests (BMD data) were used to determine statistical significance, defined as p≤0.05.
RESULTS: Mean (± SD) age at study enrollment was 33.4 ± 3.0 years. Pharmacokinetic parameters (mean ± SD) were:

Time Period	Heparin (U/day)	Cmax (U/ml)[a]	Cmin (U/ml)	tmax (hr)	t1/2 (hr)	AUC_{0-t} (U*hr/ml)[b]	$Cl_{apparent}$/kg (mL/hr/kg)
Pre-pregnancy	2500	0.32 ± 0.09	0.02 ± 0.01	2.1 ± 1.0	10.1 ± 7.6	2.50 ± 0.95	17.0 ± 4.4
First trimester	2500	0.22 ± 0.13	0.06 ± 0.05	3.8 ± 4.1	11.7 ± 7.6	1.99 ± 0.88	25.3 ± 16.7
Second trimester	5000	0.33 ± 0.12	0.05 ± 0.02	3.7 ± 1.3	5.2 ± 3.1	3.32 ± 1.28	24.5 ± 11.7
Third trimester	7500	0.47 ± 0.11	0.07 ± 0.06	4.8 ± 1.1	7.4 ± 1.8	5.52 ± 1.52	17.7 ± 2.6

[a]p<0.05 between pre-pregnancy vs 1st trimester, pre-pregnancy vs 3rd trimester, 1st vs 2nd trimester, 1st vs 3rd trimester, and 2nd vs 3rd trimester; [b] p<0.05 between pre-pregnancy vs 3rd trimester, 1st vs 2nd trimester, 1st vs 3rd trimester, and 2nd vs 3rd trimester

Pre-pregnancy and 3-month postpartum mean BMD values were 1.25 ± 0.11 g/cm^2 and 1.16 ± 0.12 g/cm^2, respectively (lumbar spine, L2-L4; p=0.02) and 0.99 ± 0.07 g/cm^2 and 1.02 ± 0.08 g/cm^2, respectively (femoral neck; p=0.93).
CONCLUSIONS: In females with APS, our current empiric dosing regimen of LMWH yielded the least and greatest drug exposure (i.e., AUC, Cmax) during the first and third trimesters of pregnancy, respectively. This interesting preliminary observation, if confirmed, could lead to a change in the clinical management of pregnant patients with APS. Although pre-pregnancy and postpartum lumbar spine BMD values were statistically different, the clinical significance of this finding is questionable and requires validation in healthy pregnant women who are not on heparin therapy.

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.

284E. Evaluation of a pharmacy-based, adult inpatient pneumococcal and influenza immunization pilot program. *Sharya Vaughan Bourdet, Pharm.D.,* Leslie Driver, Pharm.D., Meera Kelley, M.D., John Rublein, Pharm.D., Dennis M. Williams, Pharm.D.; University of North Carolina Hospitals; University of North Carolina Chapel Hill, NC.

PURPOSE: The purpose of this project was to implement a pharmacy-based, adult inpatient pneumococcal and influenza immunization pilot program utilizing standing orders and to determine if such a program increases vaccination rates among high-risk patients.
METHODS: Patients admitted to three medicine services (general, pulmonary and infectious diseases) were included in a pharmacist intervention group to determine eligibility for vaccination. Pharmacists performed patient assessment, education and completed a vaccine standing order for eligible patients. The comparative group was three medicine services not included in the pilot program. Data collected during January and February 2001 included total number of admissions, number of patients assessed by a pharmacist, number of patients at high-risk for pneumococcal and influenza infection, number of patients vaccinated during hospitalization, and number of patients previously vaccinated.
RESULTS: Of total admissions, 442 (81.5%) and 478 (88.2%) in the intervention group and 608 (79.9%) and 659 (86.6%) in the observation group had one or more indications for pneumococcal and influenza immunization, respectively. Pharmacists screened 47% of intervention patients. Among patients screened, 46% and 50% were previously immunized with pneumococcal and influenza vaccines, respectively. For patients with indications for immunization, more patients in the intervention group received pneumococcal vaccine (14.9% vs 0.5%, p<0.0001) and influenza vaccine (9.8% vs 0.7%, p<0.001) while hospitalized as compared to patients in the observation group.
CONCLUSION: An inpatient immunization pilot program using standing orders completed by pharmacists increased vaccination rates among patients with indications for pneumococcal and influenza immunization. Available resources are an important determinant of program success.
Presented at the Midyear Clinical Meeting of the American Society of Health-System Pharmacists, Las Vegas, Nevada, December 3-7, 2000.

285. Adverse drug reaction reporting using handheld computer technology. *Valerie Relias, Pharm.D., BCOP,* Heather Abourjaily, Pharm.D., Rosy Suleman, B.Sc., Mark Klee, Pharm.D., Frank Massaro, Pharm.D.; Massachusetts College of Pharmacy and Health Sciences; New England Medical Center, Boston, MA.

PURPOSE: To define, implement, and evaluate the utility of integrating Palm Pilots (Palm V™) into existing clinical pharmacy practices in an academic medical center to collect information about actual and potential adverse drug reactions (ADR).
METHODS: The research team was composed of five pharmacists with clinical practices in general medicine, cardiology, surgical intensive care, pediatrics, and bone marrow transplantation. The team, in collaboration with other pharmacists, physicians, nurses, and risk managers identified the elements needed for an electronic adverse drug reaction reporting program. Patient demographics, timing of the ADR, drugs implicated, interventions required, and patient outcomes were identified as key elements. Using Pendragon® software, an ADR reporting form consisting of 25 fields was developed to gather information useful in understanding ADRs. The research team tested and modified the form to ensure completeness and ease-of- use. Once finalized, the form was downloaded onto the Palm Pilots of the research team.
RESULTS: Collection of ADR data using the new program is underway. Information about actual and potential ADRs will be downloaded from clinicians' Palm Pilots® into a single Access™ database for analysis. After the initial test phase, the form will be disseminated to the entire pharmacist staff. Knowledge gained from the new program will be used to improve the safety of the medication system.
CONCLUSION: Experience with the use of Palm Pilots and their feasibility for use in clinical applications will be evaluated. This new technology may provide a more convenient and practical method for gathering information about ADRs.

286. Implementation of a pharmacist-managed cardiovascular risk reduction service. *Rebecca E. Barrington, Pharm.D.,* Kim A. Thrasher, Pharm.D., BCPS, Bruce R. Canaday, Pharm.D., BCPS, FASHP; Coastal Area Health Education Center; New Hanover Regional Medical Center, Wilmington, NC.

PURPOSE: To enhance primary and secondary prevention of coronary heart disease (CHD) efforts in an internal medicine outpatient clinic through the implementation of a pharmacist-managed risk reduction service.
METHODS: Based on an IRB-approved evaluation of 93 patients (retrospective chart review and patient questionnaire) in which multiple opportunities for improvement in CHD risk reduction efforts and patient education were identified, we initiated a pharmacist-managed cardiovascular risk reduction service.
Prior to clinic appointments, the ten-year risk of CHD was derived for all patients utilizing the Framingham Heart Study calculation. Patients with preexisting or an above average risk of CHD were enrolled into the service for more extensive review which addressed six major modifiable risk factors. Pharmacist-generated recommendations for primary and secondary CHD prevention were placed in patient charts for physician consideration. Additionally, educational materials, referral forms for nutrition therapy, and information regarding local weight loss and smoking cessation programs were provided.
RESULTS: There were 254 patients screened before appointments and 86 enrolled in the service. Ninety-one recommendations were made regarding medication changes or medication-related laboratory monitoring. Physicians accepted 97.8% of recommendations; approximately 60% were implemented the day of the clinic visit. Thirty-four medication-related laboratory tests were ordered, 11 new preventative medications were started, 5 medication doses were increased, and 4 patients referred for nutrition therapy.
CONCLUSIONS: Physicians were highly receptive to pharmacist input resulting in multiple interventions to prevent CHD. Cardiovascular disease prevention efforts in an internal medicine outpatient clinic can be enhanced by a pharmacist-managed cardiovascular risk reduction service.

287. Clinical pharmacy involvement in dofetilide dosing program at the University of Pittsburgh Medical Center Health System. *Amy L. Seybert, Pharm.D.*; University of Pittsburgh Medical Center Health System, Pittsburgh, PA.

PURPOSE: To describe education and monitoring for a newly approved antidysrhythmic agent, dofetilide, in a healthcare system.
METHODS: A multidisciplinary team, consisting of cardiologists, electrophysiologists, nurses, and a clinical pharmacist, designed a program for utilization of dofetilide in atrial dysthymia patients. The healthcare system is a 15-institution system, which includes major academic, tertiary care, and community hospitals. The dofetilide program included education of physician, nursing, and pharmacy staffs throughout the system. All patients prescribed dofetilide were assessed for appropriateness, electrocardiogram, and renal function. Verification of insurance coverage was obtained prior to admission. Patients were also educated about dofetilide usage, adverse effects, and drug interactions prior to initiation of therapy. An electrocardiogram was obtained after each dose of dofetilide and renal function was monitored daily.
RESULTS: FDA requirements were met for each institution and patient. Nine patients were prescribed dofetilide in a 6-month time period. Four patients continued dofetilide therapy at the initial dose administered. Two patients had dofetilide dosage adjustments, but continued on therapy. Two patients tolerated only one dose of dofetilide, due to prolonged QT intervals. One patient was prescribed dofetilide, but did not have an appropriate indication. This patient did not receive dofetilide. Four cardiologists have undergone appropriate education and documentation to prescribe dofetilide.
CONCLUSION: Clinical pharmacy involvement in a dofetilide dosing program is an invaluable component of safe and effective therapy of atrial dysrhythmias. With diligent monitoring of patient therapy and education staff, dofetilide therapy can be a useful addition to a large healthcare system.

288. Augmenting physician utilization of a pharmacy-managed lipid clinic: clinical outcomes. *Andrew F. Kelliher, M.S., R.Ph., M.B.A.,* James A. Vieira, Pharm.D., Robert G. Henault, R.Ph., C.D.E., George Alexis M.S., R.Ph., Lisa A. Marchesseault, Pharm.D.; VA Boston Healthcare System, Boston, MA.

PURPOSE: To increase physician awareness of an existing pharmacy managed lipid clinic, identify patients with hyperlipidemia, increase referrals of patients to the lipid clinic and improve patient lipid profiles.
METHODS: An electronic memo describing the services offered by the Pharmacy Lipid Clinic was sent to all primary care physicians (PCPs). Included in the memo were the average LDL-C rate reductions achieved by patients already enrolled in the clinic. A computer-generated report identified all participating physician's patients with LDL-C cholesterol levels in the past 3 months ≥ 60 mg/dl. Pharmacists electronically sent each participating PCP a list of their eligible patients, offering enrollment in the lipid clinic. PCPs wishing to enroll their patients needed only to respond to the electronic mail. Pharmacists subsequently contacted and scheduled patients for a clinic appointment.
RESULTS: We identified over 100 patients as a result of our initial computer search for patients with LDL-C levels ≥160 mg/dl. Of these, 33 patients met the inclusion criteria and were referred to the lipid clinic by their PCPs representing a substantial increase in physician referrals. Appointments were scheduled for 30 of the 33 patients.
To date, baseline and follow up data has been collected for 11 patients after a 6-8 week follow up. There was a 33% or 62 mg/dl ($p<0.002$) reduction in average LDL-C compared to baseline. There were no reports of adverse events.
CONCLUSIONS: Ease of referral and increased physician awareness resulted in an increased number of referrals to our clinic. Significant LDL-C reduction was also achieved.

289. A cost-reduction program for propofol in a surgical intensive care unit. *Karen O. Petros, Pharm.D.,* Nancy W. Knudsen, M.D., Mark W. Sebastian, M.D.; Duke University Medical Center, Durham, NC.

PURPOSE: As part of a hospital-wide initiative to reduce drug costs/usage in the intensive care units (ICU), a program was undertaken to reduce the use of propofol in our Surgical ICU. Previously, guidelines had been developed and implemented and were effective as long as timely feedback was provided to prescribers. Appropriate patient selection had been one of the earlier program's goals however length of therapy remained a problem. With the addition of in-house Attending Physicians to the ICU around-the-clock, a new program was implemented in which the approval of the attending physician was required for propofol usage. Additionally, a clinical pharmacist reassessed the need for therapy on rounds each morning.
METHODS: Propofol use was reviewed for the previous two quarters and the new restricted policy implemented in July 2000. Orders were screened for appropriate signature and usage at the time of prescribing. A rounding pharmacist reviewed usage data on a daily basis. Feedback was provided to the ICU Directors and data were regularly presented at attending physician meetings.
RESULTS: Total usage was reduced by 54% during the study period. This resulted in an acquisition-cost reduction of $226,683/6 months. Continued surveillance has demonstrated a sustained effect of this program. The multi-trauma patient with head injury was identified as a target group for shortening length of therapy. The current median length of therapy in this group is 32 hours.
CONCLUSION: A focused program including pharmacist review, attending physician participation and timely feedback to prescribers was successful in reducing the use of propofol.

290E. Pharmacoeconomic impact of a pharmacist-managed automatic intravenous to oral conversion program. *Joseph L. Kuti, Pharm.D.,* Thuy N. Le, Pharm.D., Charles H. Nightingale, Ph.D., David P. Nicolau, Pharm.D., Richard Quintiliani, M.D.; Hartford Hospital, Hartford, CT.

PURPOSE: The economic advantage of intravenous (IV) to oral (PO) antibiotic conversion programs has been documented in numerous studies but have required pharmacists to contact the physician to encourage oral streamlining. Unfortunately, no study has ever assessed the implications of having the pharmacist convert appropriate patients on their own, which could further reduce costs. Therefore, we compared the economic and clinical outcomes for the standard of care at our institution with that of an active pharmacist conversion program (ACP) for the antimicrobial levofloxacin.
METHODS: Criteria were developed to identify candidates for IV to PO conversion. A prospective observational study (POS) assessing the standard of care was conducted over 2 months and was compared with the ACP. Data were collected on day of meeting criteria, day of conversion, reconversion rate, LOS, and cost per treatment (drug plus supply). All patients receiving IV levofloxacin were evaluated unless they were in the intensive care unit.
RESULTS: Forty-nine patients were evaluated in the POS and 66 in the ACP. Patients met criteria for conversion on day 2 in both groups. The average day of conversion for the POS and ACP groups was Day 7 and 3, respectively ($p=0.009$). LOS was similar between groups. Cost per patient for levofloxacin treatment was $158 and $90 in the POS and ACP, respectively ($p=0.002$). One patient in the ACP was reconverted to IV levofloxacin.
CONCLUSION: A pharmacist-managed automatic IV to PO conversion program reduced the cost of drug therapy for patients treated with levofloxacin without compromising clinical outcomes.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

291E. Diabetes partners in care pilot project: patient-focused diabetes education and management in the community pharmacy practice setting. *James J. Sterrett, Pharm.D.,* Deborah S. Carson, Pharm.D., Kit Simpson, Ph.D., Sarah J. Rider, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Diabetes mellitus (DM) is a significant problem in the U.S. and particularly prevalent in South Carolina. This project aims to determine whether community pharmacists, equipped with diabetes management certificate training can: 1) positively impact the adherence to the American Diabetes Association (ADA) Clinical Practice Recommendations; 2) improve patient quality of life; and 3) positively affect surrogate markers of diabetes control and predictors of long-term complications in South Carolina state employees with DM.
METHODS: A 1-year retrospective and 2-year prospective case-controlled study is being performed with 257 enrolled patients and 42 study pharmacists. Community pharmacists who completed an 80-hour diabetes certificate training program were eligible to participate in the pilot. South Carolina state employees who met the following criteria were eligible: enrolled in the state health benefits plan for at least 1 year, diagnosed with DM, at least 18 years of age, not pregnant, and receiving prescriptions for oral antidiabetic medications and/or insulin.
RESULTS: Of the successfully enrolled patients, 57% either had no HgA_{1c} value recorded in their medical record over the prior year or had a value greater than the ADA goal of 7%, reflecting a needed improvement in care to reach guideline standards. Baseline data also reflected low documentation to other ADA standards of care: 27% had a recorded foot examination, 50% had a dilated eye examination, 32% were on daily aspirin, and only 25% were on an angiotensin-converting enzyme inhibitor. The initial data also reflect a high (41%) patient drop-out rate before the second pharmacy visit. Initial (1 year) results demonstrated overall improvements (decreases) in the surrogate markers: HgA_{1c} (0.61%), fasting blood glucose (17.5 mg/dl), systolic blood pressure (2.89 mm Hg), diastolic blood pressure (1.75 mm Hg) and weight (4.2 lbs).
CONCLUSIONS: Using specially trained pharmacists in the community setting may be associated with positive patient outcomes, however, the method of patient selection appears to be important in patient participation and retention.
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292. Development of a culture follow-up program in the emergency department (ED). *Kevin O. Rynn, Pharm.D., DABAT,* Frank L. Hughes, Pharm.D.; Rutgers University; Robert Wood Johnson University Hospital, New Brunswick, NJ.

PURPOSE: The Robert Wood Johnson University Hospital ED has over 60,000 patient visits a year. Many patients are discharged the same day while some laboratory tests, such as cultures and sensitivities, may not return for up to 72 hours. The objective was to develop a pharmacist managed culture follow up program in the ED.

METHODS: Develop a policy and procedure for the appropriate assessment, treatment, and documentation of positive cultures obtained from discharged ED patients. The assessment included obtaining laboratory results, reviewing patient records for appropriate empiric treatment, and discussing cases with the ED attending when further intervention was required. All positive cultures were documented in a logbook and any pharmacist intervention required documentation in the patient's ED chart.
RESULTS: Between August 1, 2000 and April 30, 2001, 265 patients were assessed. Results from 175 urine, 34 throat, 17 blood, 10 wound, 3 nasal passage, 2 stool, 2 CSF, and 2 peritoneal dialysate fluid cultures were analyzed. One monospot, 3 Lyme titers, and 3 RPR titers were also analyzed. One hundred and ninety-eight patients (75%) required no further follow-up. Of the remaining patients, 7 required new prescriptions, 4 were admitted to the hospital, 3 were asked to return to the ED, 15 followed-up with their primary care physician, 15 were not able to be contacted and letters were sent, and 23 were asymptomatic on follow-up.
CONCLUSIONS: Implementation of the program provides a new role for a pharmacist in the ED while potentially decreasing morbidity and mortality.

293. Clinical pharmacists' effectiveness in intensive diabetes care management integrating the chronic care model. *Theresa S. O'Young, Pharm.D.,* Cynthia Brennen, Pharm.D., MHA, Kathy Mertens, R.N., MPH, Daniel Lessler, M.D., MHA; Harborview Medical Center; University of Washington; Seattle, WA.

BACKGROUND: The Institute of Healthcare Improvement describes the chronic care model as a prepared practice team interacting with an informed activated patient resulting in optimal patient care.
PURPOSE: To evaluate the effectiveness of a pharmacist who facilitated medication management and a patient empowerment philosophy on clinical outcomes and self-management in patients with diabetes.
METHODS: A clinical pharmacist, in an internal medicine clinic, university affiliated county hospital, trained in motivational interviewing and the chronic care model worked collaboratively with providers to initiate and titrate medications, and partner with patients to set behavior modification goals. Seventy-four patients referred to the pharmacist for disease state management between January 1 and December 31, 2000 consisted of those interested in improving diabetes control or glucoses not optimally controlled as defined by HgA1c level. Self-management was promoted through diabetes education and problem solving around achieving goals. Patient care was delivered by clinic visit, telephone follow up and in an ad hoc manner through a consistent presence in clinic. Changes in glucose control (HgA1C), blood pressure (<130/85), and documentation of both monofilament foot exam and self-management goal were evaluated.
RESULTS: Sixty-six percent of patients had a decrease of HgA1c (0.9%), sixty-six percent met blood pressure goal, sixty-nine percent had a documented foot exam, sixty-six percent had a documented self-management goal.
CONCLUSION: A clinical pharmacist using the chronic care model showed improvement in clinical outcomes in diabetes care.

294. Impact of electronically transmitted recommendations on glycemic control in patients with type 2 diabetes mellitus. *Kenneth R. Eugenio, Pharm.D.,* Andrew F. Kelliher, M.S., R.Ph., M.B.A., Robert G. Henault, R.Ph., C.D.E., George Alexis, M.S., R.Ph., Paul R. Conlin, M.D.; VA Boston Healthcare System, Boston, MA.

PURPOSE: Data are limited regarding the impact of electronically transmitted recommendations on glycemic control. This study was conducted to assess the impact of recommendations sent via e-mail on the HbA1c levels of patients with poorly controlled type 2 diabetes mellitus.
METHODS: Patients were screened to identify those with 1) HbA1c levels ≥ 9%, 2) routine follow-up with a primary care provider (PCP), and 3) no change in diabetes therapy within 60 days. Patient records were reviewed for relevant history, laboratory markers, and current diabetes therapy. A recommendation was then sent via e-mail to the patient's PCP. Patients with similarly elevated HbA1c values, in whom recent action had been taken to improve glucose control, were also identified to serve as a control group.
RESULTS: Thirty patients met the inclusion criteria. The average age was 66 years (range 41-87); all were male. Twenty-four recommendations were accepted, 1 was declined, and 5 received no response. Follow-up HbA1c levels were available for 21 patients after a mean of 6.3 months. E-mail recommendations resulted in significantly decreased HbA1c values (10.0 ± 1.0% to 8.2 ± 1.2%, $p<0.001$). In comparison, 35 patients who were actively managed by their PCP had a 1.6% reduction in HbA1c levels (10.2 ± 1.1% vs 8.6 ± 1.3%, $p<0.001$).
CONCLUSIONS: Recommendations sent via e-mail were readily accepted and proved to be effective in improving diabetes control. This type of patient management strategy may result in early and significant changes in HbA1c levels in patients at high-risk for diabetes complications.

295. Meeting the challenge of providing and documenting comprehensive education to all patients with diabetes in a primary care clinic. *Suzanne G. Gielow, Pharm.D.,* Ruth A. Seabaugh, Pharm.D., Theresa R. Prosser, Pharm.D.; Saint Louis College of Pharmacy, Saint Louis, MO.

INTRODUCTION: National standards for diabetes education require documentation of educational assessments, interventions, plans, and follow-up in a permanent record. Many patients are not motivated to attend extra group/individual educational sessions. During brief physician visits, it is difficult to deliver in-depth information. For comprehensive education, topics discussed with each patient need to be tracked. Teaching by multiple pharmacists, residents, and students may contain inconsistencies and be duplicative or incomplete. Our purpose is to systematically provide and document a comprehensive curriculum to all patients with diabetes in our primary care clinic.
METHODS: Our curriculum is based on national standards and is broken into brief topics (most are 5-15 minutes in duration). For each topic, (e.g., HgA1c, target organ damage, medications, self-monitoring) standardized "teaching points" and educational materials/samples are defined. An educational flow sheet tracks the topics discussed, dates of instruction/reassessments, and educator.
RESULTS: Reviewing the flow sheet, helps track the topics previously discussed/reassessed and those remaining. Diabetic education is provided and documented more routinely at each patient visit. With standardized teaching points, rotating pharmacy students can provide consistent diabetic education with less direct supervision. One year later, it is easier to perform quality assurance on diabetic education. The number of different topics discussed per patient and documentation of diabetic education has increased (from 25 to 84% of patient records).
IMPLICATIONS: Our diabetes educational curriculum assists in delivering comprehensive, standardized diabetic education to all patients. The flow sheet facilitates performing quality assurance, tracking and reassessing patients' educational needs and improves documentation.

296. Use of diabetic screening form and registry to improve process indicators and outcomes in a primary care clinic. *Suzanne G. Gielow, Pharm.D.,* Ruth A. Seabaugh, Pharm.D., Theresa R. Prosser, Pharm.D.; Saint Louis College of Pharmacy; Saint Louis, MO.

PURPOSE/INTRODUCTION: Our goal was to improve diabetes care by providing physicians and staff with 1) necessary interventions prior to each patient visit 2) timely feedback regarding overall performance on process indicators.
METHODS: A screening form with nationally recognized diabetes process indicators was developed. Pharmacists prospectively used the screening form to identify pertinent interventions (e.g., recommend referrals/laboratory, document smoking status/foot exams). A registry including concurrent data on indicators from all diabetic patients was established. After 1 year, data on diabetic indicators was compared to that from a baseline retrospective chart audit 20 months earlier.
RESULTS: All diabetic patients (n=215) were evaluated. Prospective screening identified 46 additional patients since the initial audit. The percentage of charts with documentation of annual ophthalmology exams (26% vs 38%), foot checks (25% vs 77%), patient education (25% vs 84%) and tobacco status (23% vs 94%) improved. Of the smokers identified, 80% were counseled to quit. Appropriate use of renal protective agents (83%) and screening for microalbuminuria (69%) were unchanged. Patients with a HgA1c less than 8% unchanged (50%), but the average HgA1c decreased from 8.9 to 7.9%. The percentage of patients with a diastolic pressure less than 90 mm Hg increased (46 vs 92%). The up-to-date statistics in the registry were used to provide frequent, ongoing feedback.
IMPLICATIONS: By using a diabetic screening form and registry, pharmacists can improve performance on process indicators and the quality of care. Organizing indicator data into a diabetic registry can provide a method for ongoing feedback to staff and physicians.

297. Interventional tool to enhance appropriate antibiotic use and increase quinolone susceptibility of *Pseudomonas aeruginosa*. *Cynthia L. Feucht, Pharm.D., BCPS,* Louis B. Rice, M.D.; Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH.

PURPOSE: A retrospective review was done to evaluate the appropriateness of intravenous (IV) vancomycin and quinolone antibiotics. Based on this, a multidisciplinary, prospective intervention program was implemented to improve empiric utilization of these antibiotics, decrease inappropriate dual gram-negative coverage and increase quinolone susceptibilities of pseudomonas.
METHODS: A computerized review was performed for patients receiving IV vancomycin and quinolones for 1998 in a Veterans Affairs Medical Center. In June of 1999, guidelines were disseminated and an intervention program was initiated with a monthly conference to medical residents regarding antimicrobial resistance and local hospital practices. Concurrently, a prospective review of new orders was assessed by the clinical pharmacist and interventions performed when inappropriate use occurred. Total IV antibiotic costs for selected agents were evaluated yearly (1998-2000) to determine if a decrease in quinolone utilization resulted in an increased use in other antimicrobials.
RESULTS: Courses of vancomycin increased minimally from 1998 to 2000 with an increase in appropriate use from 28% to 33%. Discontinuation of

inappropriate vancomycin by day five increased from 37% to 48%. Courses of IV quinolones decreased by 37% and dual gram-negative coverage decreased by 26% from 1998 to 2000. Pseudomonas susceptibilities to quinolones decreased from 54% in 1998 to 47% in 2000. An antibiotic cost reduction of $62,000 was observed.
CONCLUSIONS: Education of physicians through monthly conferences and personal interventions resulted in an increase in appropriate empiric antibiotic utilization and a decrease in the duration of inappropriate use. The program did not have an impact on pseudomonal quinolone resistance.

298. Implementation of pharmacist-managed levofloxacin sequential conversion program in a 512-bed acute-care hospital. *Mary V. Caputi, Pharm.D., M.S.*; Owen Healthcare, Inc.; Manatee Memorial Hospital, Bradenton, FL.

PURPOSE: To describe development and implementation of pharmacist-initiated sequential conversion of intravenous (IV) levofloxacin (LQ) to the oral dosage form when inclusion criteria are met. Anticipated benefits include a reduced length of IV therapy, cost-savings, and a neutral to positive effect on patient outcome.
METHODS: The program was developed in collaboration with infectious diseases specialists in response to the levofloxacin medication use evaluation that documented a 6.3-day length of IV administration. The Pharmacy & Therapeutics Committee, Infection Control Committee, and Medical Executive Committee approved the protocol. Patients are eligible for conversion after 24-48 hours of IV administration if all criteria are met; the IV dose is converted milligram-per-milligram to the oral form. Criteria include: patient afebrile for at least 24 hours, has a functioning GI tract, is tolerating oral medications and nutrition, and resolution of signs and symptoms of infection. Required chart documentation by the pharmacist includes a progress note, medication order for the conversion, notification placed on chart, and completion of an outcome tracking form. Data collection includes demographic information, indication for IV LQ, IV length of therapy, oral length of therapy, cost-savings, reconversion rate (converted back to IV by the physician). Pharmacoeconomic benefit will be assessed by cost savings for the days on oral therapy ([IV cost B oral cost] x # days on oral LQ). Outcome evaluation will be based upon the reconversion rate.
RESULTS: Program implemented May 2001, data will be presented at the meeting.

299. Antimicrobial susceptibility trends from 1990-2000: preliminary results of the antimicrobial resistance management (ARM) program. *John G. Gums, Pharm.D.*; University of Florida, Gainesville, FL.

PURPOSE: This ongoing study was established to document trends in antimicrobial susceptibility patterns in U.S. hospitals and identify relationships between antibiotic use and resistance rates.
METHODS: Data from 1990-2000, in the form of antibiograms and sensitivity reports from hospitals across the United States, were reviewed for resistance rates. In-patient and outpatient isolates were represented. A web-based analysis tool was developed to examine trends in resistance for individual hospitals, hospital systems, and selected geographic quadrants of the United States.
RESULTS: To date, 88 hospitals (66 non-teaching, 22 teaching) have submitted 10,315,361 total isolates. Isolate numbers per organism ranged from 289 (VRE) to 4,930,449 (E. coli). P. aeruginosa resistance was documented to ciprofloxacin (25.52%, n=115,545), imipenem (14.24%, n=110,894), gentamicin (21.21%, n=131,079), and ceftazidime (11.85%, n=133,881). E. coli resistance was noted to ampicillin (35.95%, n=296,583), ampicillin-sulbactam (30.19%, n=243,785), and piperacillin (30.69%, n=234,129). There was no surrogate evidence for E. coli-induced ESBL activity (cefazolin susceptibility 92.49% vs ceftriaxone susceptibility 99.55%). S. aureus resistance is accelerating: ciprofloxacin (38.24%, n=155,653), levofloxacin (38.31%, n=60,838), and erythromycin (72.15%, n=227,150). The overall level of MRSA was 36.67% in 210,310 isolates. The documented level of VISA isolates was 0.04%. S. pneumoniae non-susceptibility to penicillin was 37.45% among 21,127 isolates. Significant differences were noted between cefotaxime susceptibility (69.20%) and ceftriaxone susceptibility (80.41%) to pneumococcus.
CONCLUSION: Antimicrobial resistance is accelerating. Recognition of local resistance patterns is essential to determine strategies for intervention. Ongoing efforts through the ARM program will help institutions identify and solve growing resistance problems.

300. The formulary management system and decision-making process at Horizon Blue Cross Blue Shield of New Jersey: review of osteoporosis and emerging treatment options. *Saira A. Jan, M.S., Pharm.D.,* Terry D. Leach, R.Ph., Alan F. Kaul, R.Ph., M.S., MBA, FCCP; Horizon Blue Cross Blue Shield of New Jersey, Newark, NJ; Rutgers University College of Pharmacy, Newark, NJ; Medical Outcomes Management, Foxborough, MA; University of Rhode Island, Kingston, RI.

We describe the formulary evaluation, selection, and management processes at Horizon BCBSNJ using the disease of osteoporosis and the bisphosphonate class of drugs as examples. Among the criteria considered for adding a drug to formulary are evidence-based medicine, comparative efficacy, clinical experience, safety, dosage interval, adverse drug reactions; dosage forms, potential utilization and cost; and pilot in-house outcomes studies. An overview of osteoporosis treatment options will be presented with a detailed review of bisphosphonates. Selection of an appropriate bisphosphonate for formulary inclusion can be a difficult task because of the limited comparative literature and differences in relative potencies and dosing regimens. As part of its commitment to promoting "excellence in women's health care", Horizon BCBSNJ's Quality Management/Outcomes Measurement Department began distributing a package of patient educational brochures on menopause management to 20,000 female members aged 45-64 in its Horizon HMO insurance plan. The Pharmacy Services Department and the Quality Management/Outcomes Measures Department also developed a trifold brochure as part of an educational outreach program to increase provider awareness of the health consequences related to osteoporosis and the benefits and risks of pharmacotherapy. Based on its evaluation, the P&T Committee at Horizon BCBSNJ elected to add risedronate to its formulary that already included alendronate. Horizon's Pharmacy Services initiated an in-house study comparing their fracture rates. This study data will provide further information on clinical outcome of these agents when they are re-evaluated and help to understand the tolerability and effectiveness among different doses of bisphosphonates in ambulatory populations in real-life settings.

301. Creation of anemia team at a university-based renal dialysis center. *Ruth Ann Subach, Pharm.D., BCPS,* Sandra Loskill, R.D., Cyril H. Barton, M.D.; Western University of Health Sciences, Pomona, CA; University of California at Irvine, Orange, CA.

Anemia is a nearly universal complication of renal failure. Our facility cares for approximately 140 hemodialysis (HD) and peritoneal dialysis (PD) patients. Management of anemic ESRD patients in an academic setting is sometimes complicated by frequent changes in physician coverage. To improve the consistency and quality of anemia management at our dialysis center, we updated our anemia management protocol (AMP), created a comprehensive database, and developed an Anemia Team.
The prior AMP was reviewed, updated to meet national standards, and expanded to include more information about medications use and monitoring. The protocol was approved 8/14/00, and instituted shortly thereafter.
The anemia database contains patient demographics, selected clinical information, anemia-related laboratory values and medications. The database is maintained weekly by the nephrology pharmacist.
The Anemia Team consists of the pharmacist, dietician, nurse, billing administrator, and physicians. The Anemia Team meets twice monthly for review of HD patients' data, and once monthly during clinic for PD patients. The team makes decisions about erythropoietin and iron dosing taking into consideration numerous patient-specific factors. Decisions are recorded in the database, and orders are placed in the chart for all patients within 24 hours of the meeting, streamlining the ordering processing. Database maintenance is time consuming, but allows the team to monitor outcomes, taking into consideration changes in patient condition and medications.
We have improved our anemia outcome data, and our database allows us to analyze how we can improve our outcomes further. Further outcome data and the AMP will be presented at the poster.

302. Establishment of an interdisciplinary headache clinic in a primary care setting. *Kristin W. Weitzel, Pharm.D.,* Sandra F. Seymour, Ph.D., ARNP, Rhondda Waddell, M.S.W., LCSW, Michael Huey, M.D.; University of Florida, Gainesville, FL.

PURPOSE: To establish an interdisciplinary pharmacist-run headache clinic in a medically underserved primary care setting.
METHODS: Patients are referred to the headache clinic by their primary care provider (PCP), either family nurse practitioner or physician. During the first visit, the pharmacist performs a medication review and headache history. Headache diagnosis is confirmed through consultation with the patient's PCP and patient is provided with a headache diary. The patient returns in two weeks, at which time the headache diary is reviewed and pharmacotherapy recommendations are presented to the PCP, with appropriate action taken. Patients may also be referred to psychology, neurology, or social services. Patients continue to follow up in clinic every 3 months or more often as needed.
RESULTS: At one year, seventeen patients are enrolled. Mean patient age is 39 years (range 14 to 61), sixteen of which are female. Headache types include migraine (41%), chronic daily headache with mixed presentation (35%), mixed presentation (18%), and tension-type (6%). Pharmacotherapy changes implemented include prophylaxis (47%), abortive therapy (18%), optimization of current prophylactic/abortive drug regimen (12%), or other (35%). According to headache diaries or patient report, headache frequency and/or severity has decreased since initial headache visit in 65% of patients. Feedback from providers in the clinic has been positive.
CONCLUSIONS: Pharmacists can have a role in headache management. This program has had a positive impact on therapy in a limited number of patients and has been well received by other health care providers in this inter-disciplinary setting.

303. Pharmacist-directed diabetes clinic in a chain pharmacy. *Nazir Sleiman, R.Ph., D.E.,* Linda A. Jaber, Pharm.D., Sandra Nowak, Pharm.D., Richard L. Slaughter, M.S., FCCP; Wayne State University, Detroit, MI; Rite-Aid Corporation, Harrisburg, PA.

The purpose of this report is to describe the impact of a pharmacist run diabetes clinic operating within a Rite Aid Pharmacy. The pharmacist was trained to manage diabetic patients through the Life Scan Pharmacy Partners in Diabetes Care (PPDC) program. Patients are identified by the pharmacist or referred to him through physicians in the area. He has followed seven patients with four of these patients monitored for between 4 and 12 months. Patients are seen on a monthly basis for evaluation of control of their diabetes with these visits lasting from 50 to 120 minutes (averaging almost 90 minutes). Prior to being seen by this pharmacist diabetic control was poor with home monitored blood glucose concentrations averaging 204 g/dl (range 123-346 g/dl). The difference between the maximum and minimum observed glucose concentration (a measure of control) averaged 230 g/dl (range 108-486 g/dl). Pharmacist directed interventions included diet modification, exercise therapy and adjustment of drug therapy. At an interim evaluation the average blood glucose decreased in all patients to 131 g/dl (range 114-146 g/dl) the difference between the maximum and minimum glucose concentration decreased to 148 g/dl (range 77-268 g/dl). At final evaluation in four patients, blood glucose concentrations decreased in all patients and averaged 122 g/dl (range 100-153 g/dl) and the difference between the maximum and minimum blood glucose concentrations decreased to 123 g/dl (range 83-196 g/dl). Body mass index decreased in 3 of these 4 patients. This community pharmacist has had significant positive impact on the control of diabetic patients he has cared for through his practice within a Rite Aid Pharmacy.

304. Partnering with schools to improve community health awareness. *Melissa Somma, Pharm.D.,* Michele C. Musheno, R.Ph., M.S., Kim Kelly, R.D., Richard Martin, M.D., Michael Evanick, Pharm.D., Lisa Tomaine, Pharm.D. candidate; Wilkes University, Wilkes-Barre, PA; Geisinger Health Group-Lake Scranton, Scranton, PA.

PURPOSE: Together with a local school district, a series of osteoporosis and cholesterol screenings were conducted to form a collaborative relationship, promote a healthy lifestyle for the teachers and ultimately their students, and to evaluate satisfaction of a community-based program.
METHODS: During a 5-day period, 199 teachers voluntarily underwent venous blood draws for total cholesterol and completed a baseline health inventory survey. A pharmacist and physician team reviewed the results. Individual cholesterol results and recommendations were presented to the teachers during a 30-minute in-service performed by a pharmacist, dietitian, and pharmacy student team. On the same day, a pharmacist and students performed osteoporosis screenings using an ultrasound heal bone density device. Teachers were individually counseled on diet, exercise, and medication therapy. After the sessions, 105 teachers responded to a satisfaction survey.
RESULTS: Of the 153 patients screened for cholesterol, 45.6% were above their respective total cholesterol goals, with values ranging from 116-312 mg/dl. In addition, of the 144 patients screened for osteoporosis, only 41.3% were currently supplementing their diet with calcium and 53.5% were either at intermediate or high risk for developing a fracture. Satisfaction was high, with 98.1% of the patients intending to follow recommendations provided and 88.6% agreeing the sessions will help in educating their students.
CONCLUSIONS: Forming a partnership with schools allowed for early identification of patients at risk for coronary artery disease and osteoporosis, along with healthy lifestyle promotion. The collaborative efforts of pharmacists, physicians, dietitians, and pharmacy students were vital in the success of the program.

305. Multidisciplinary diabetes group education sessions in a community physicians' practice. *Melissa Somma, Pharm.D.,* Michael J. Fox, M.D., Diane Pachucy, R.N., Kim Kelly, R.D., Lisa Tomaine, Pharm.D. candidate; Wilkes University, Wilkes-Barre, PA; Geisinger Health Group-Lake Scranton, Scranton, PA.

PURPOSE: This program is designed to provide a multidisciplinary approach to diabetes patient education, improve patient outcomes, and offer a personalized approach to patient learning.
METHODS: Beginning in October 1999, patients with type 2 diabetes were identified by their physician and invited to participate in a comprehensive four-week educational program, covering pathophysiology, medications, herbals, self-care, diet and physical therapy. Each of the four two-hour sessions was conducted in a rural, community physicians' office by members of the healthcare team including a physician, pharmacist, dietician, nurse, and pharmacy students. Monitoring parameters included $HgbA_{1c}$, total cholesterol, triglycerides (TG), low-density lipoproteins (LDL), and blood pressure, along with medication reviews. Following each session, a patient satisfaction survey was completed.
RESULTS: Twelve-month follow-up data was available for 25 of the 47 patients enrolled. The values for $HgbA_{1c}$, total cholesterol, TG and LDL decreased by 1.35% (n=25, p<0.001), 60 mg/dl (n=9, p<0.005), 106 mg/dl (n=8, p=0.028), and 49 mg/dl (n=7, p=0.015) respectively. Throughout the program, blood pressure remained at goal, with average values less than 130/80 mm Hg. Patient satisfaction was high, with 84% agreeing that they would recommend the program to others and 72% enjoying the small group atmosphere.
CONCLUSIONS: This program may serve as a model for other community physicians' offices. These preliminary results suggest that collaborative efforts among health care practitioners can improve glucose control and lipid profiles of patients sustained over one year. These efforts may ultimately prevent morbidity outcomes. Further studies with larger numbers of patients are needed to confirm these findings.

306. Evaluation of a pharmacist-assisted tobacco cessation program in Medicaid clients. *Donna G. Beall, Pharm.D., BCPS,* Cathy Bartels, Pharm.D.; University of Montana, Missoula, MT.

PURPOSE/GOAL: Smoking cessation continues to be a high priority in health care today. Community pharmacists are in a unique position to assist in tobacco-cessation because of their accessibility. A pilot-project was developed and implemented to evaluate the impact of community pharmacists' involvement in a smoking cessation program for Montana Medicaid clients. The goal of the project was to enhance tobacco abstinence rates among clients by consultation with pharmacists certified in tobacco cessation counseling.
METHODS: Interested pharmacists were recruited and assessed. Clients were recruited and screened. The program included 6 weekly face-to-face counseling sessions and weekly phone follow-ups. Post-program follow-up was done at 6, 9, and 12 months to ascertain abstinence. Pharmacists were paid a rate of up to $300 per client. It was anticipated that 100 clients would be enrolled. Pharmacists and clients were surveyed to assess the effectiveness of the program.
RESULTS: Twenty-four pharmacists expressed interest in participating. Of these, six enrolled a total of 24 clients. One-year abstinence rate was 25%. Fourteen (58.3%) pharmacists completed the survey. Pharmacists responded that there were sufficient numbers of Medicaid clients in the community; however, clients lacked motivation to quit. Materials were helpful as well as the support of the study coordinators. Challenges that impacted the pharmacist's ability to participate in the program included lack of 1) client motivation, 2) pharmacist time, and 3) pharmacist motivation.
CONCLUSIONS: Pharmacists can have a positive outcome in the smoking cessation rate in a Medicaid population. Challenges for community pharmacists to participate in clinical services are evident.

307. Competence in the field: a Web-based survey of medical science liaisons in the pharmaceutical industry. *Tom E. Peddicord, Pharm.D.,* Antoine Richardson, Pharm.D., Scott Charland, Pharm.D., FCCP, Ken Massey, Pharm.D.; Roche, Kansas City, MO; University of Missouri at Kansas City, Kansas City, MO; Roche, Evergreen, CO; Novartis, East Hanover, NJ.

PURPOSE: Delineate the background, training, and activities of Medical Science Liaisons (MSLs) within the pharmaceutical industry.
METHODS: A web-based survey was developed at the UMKC DI Center for collecting/collating the information. A mailing was sent to the top 50 companies and the ACCP Pharmaceutical Industry PRN inviting MSL participation. Descriptive information is presented.
RESULTS: Overall, 16 companies (59 respondents) responded with MSLs being 81% Pharm.D., 7% MD, 5% Ph.D., and 7% other degrees. Twenty-two percent have obtained an MS, MBA, or MPH degree. Residency (including specialty residency) and fellowship training was completed by 66% and 32% of the respondents, respectively. Twenty-five percent of MSLs are board certified, 14% fellows in a professional society, and 48 % have an academic appointment. Fifty percent of MSL have been employed for 1-5 years and 10% for 6-10 years. Prior to becoming an MSL, 56% were in academics, 24% non-academic clinical practice setting, 10% managed care administration, and 10% an alternative practice setting. Seventy-six percent of MSL are generalists (25%) and specialists (51%) with others in managed care, professional relations, directors, and governmental agencies. Seventy-six percent reported providing academic-based lectures in the past year, 51% provided CE presentations, and 97% provided non-accredited presentations. Nineteen percent have published peer-reviewed manuscripts and 10% have published abstracts while in the pharmaceutical industry.
CONCLUSIONS: This is the first survey documenting the MSL competence with the data suggesting there is abundant training and expertise within this section of the pharmaceutical industry.

308. Adherence to the American Diabetes Association guidelines in a pharmacist-managed diabetes clinic. *Sandra N. Nowak, Pharm.D.,* Linda A. Jaber, Pharm.D.; Wayne State University; Detroit Medical Center, Detroit, MI.

PURPOSE: To assess the quality of care provided by a clinical pharmacist for patients with diabetes and the extent of adherence to the standards of care recommended by the American Diabetes Association (ADA).
METHODS: Eligible patients in a pharmacist managed referral clinic were included in the experimental group and compared to a historical control group. Patients in the experimental group received diabetes education, dietary

and exercise instructions, pharmacological therapy of diabetes and associated hypertension and dyslipidemia, and routine preventive measures. Patients in the control group received standard medical care provided by primary care physicians. Main outcome measures included glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), blood pressure, lipids, urine albumin assessment, frequency of foot examination, referral and vaccination rates, and daily aspirin therapy.
RESULTS: Sixteen patients (5 men, 11 women) with a mean ± SD age of 52 ± 13.9 years, and body mass index (BMI) of 35.2 ± 9.5 kg/m^2 were included in the experimental group. The control group consisted of 13 men and 18 women with age of 57.0 ± 14.3 years, and BMI of 33.1 ± 9.0 kg/m^2. Baseline HbA_{1c} levels were 10.5 ± 2.5% (95% CI 9.17, 11.85%) for the experimental and 7.6 ± 2.4% (95% CI 6.54, 8.41%) in the control group. More patients in the experimental group (84%) were placed on combination hypoglycemic therapies compared to those in the control group (56%). A significant decline in final HbA_{1c} from baseline occurred in the experimental compared to the control group (3.03 ± 2.14% vs 0.88 ± 2.05%, p=0.006). Similarly, FPG were significantly reduced in the experimental group (baseline, 253.0 ± 126.6; final, 152.0 ± 70.5 mg/dl, p=0.018) compared to control group (baseline, 198.9 ± 79.0; final, 183.0 ± 88.0 mg/dl). Foot examinations were performed in 75% and 6.5%, annual urine albumin measured in 87.5% and 33.3%, dietary referral made for 0% and 43.8%, and podiatry referrals made for 62.5% and 32.3% of patients in the experimental and control groups, respectively (p<0.05). No significant differences were noted in other parameters.
CONCLUSIONS: A pharmacist managed diabetes clinic positively impacts the overall management of diabetes and delivers quality of care that generally meets the ADA guidelines.

309E. Lipoprotein benefits and clinical outcomes of a pharmacist run cardiac risk reduction clinic vs usual care. *Emmanuel Saltiel, Pharm.D., FASHP,* Jeff Borenstein, M.D., Phyllis A. Kidder, Pharm.D.; Cedars-Sinai Health System; Zynx Health; Pfizer Inc., Los Angeles, CA.

PURPOSE: Cedars-Sinai Medical Group, an 80,000 member, multi-disciplinary, highly capitated medical group wanted to conduct an analysis of the treatment of secondary prevention hyperlipidemia patients to determine if there was a difference in 1) LDL goal achievement (LDL ≤100 mg/dl), 2) incidence of a second cardiac event and 3) cost of drug therapy between patients enrolled in a pharmacist-managed Cardiac Risk Reduction (CARR) clinic vs usual care.
METHODS: Secondary prevention CARR clinic patients were identified by manually reviewing all clinic patient charts. ICD-9 coding (for acute MI, angioplasty or CABG) was used to identify usual care patients. All patients identified via these methods for the years 1998-1999 were evaluated and followed forward. A total of eighty-eight charts were reviewed. Seventy patients met the inclusion criteria indicated above (18 were incorrectly coded). Goal attainment was determined by the last lipid panel available. Data was analyzed in Microsoft ACCESS.
RESULTS: The CARR patients had a higher percentage of goal achievement (53% vs 33%, p=NS) and had fewer second cardiac events (10% vs 19%) as compared to usual care. Additionally, the average monthly medication cost was less for the CARR patients than usual care ($42.15 vs $66.15). Further economic analyses will be presented.
CONCLUSION: The results of the study were utilized to demonstrate the value of the clinic with the goal of increasing referrals and also as a physician education tool. This study also demonstrates the value of pharmacists supporting a private practice medical group in managing high-risk patients with hyperlipidemia.
Presented at the Annual Meeting of the American Society of Health-System Pharmacists, Los Angeles, CA, June 3-6, 2001.

310. Measuring treatment outcomes of a pharmacist-managed hypertension clinic. *Eva M. Vivian, Pharm.D., BCPS,* Ross Gombiner, M.D., Sandy Levine, M.D.; University of the Sciences; Veterans Affairs Medical Center, Philadelphia, PA.

PURPOSE: This study was conducted to determine if pharmaceutical care provided by a pharmacist-managed hypertension clinic resulted in better treatment outcomes as compared to traditional health care from a primary care physician. Treatment outcomes were measured by changes in: 1) compliance, 2) blood pressure, and 3) patient satisfaction.
METHODS: Fifty-six uncontrolled hypertensive patients were randomly assigned to the treatment group or control group for six months. Treatment group patients were scheduled monthly to see a clinical pharmacist who made appropriate medication changes, dosage adjustments and provided medication counseling in accordance with the JNC VI hypertension guidelines. The treatment group only received care for conditions unrelated to hypertension from their primary care physician. The control group received care from their physician and brief counseling from a staff pharmacist. A compliance evaluation survey and Short Form 36 was used to measure changes in compliance and patient satisfaction.
RESULTS: The mean changes in systolic blood pressure from baseline for the treatment and control groups were -18.4 (95% CI -26.3, -10.5) and –3.98 (95% CI -11.8, 3.79) respectively (p=0.01). The mean changes in diastolic blood pressure from baseline for the treatment and control groups were –12.38 (95% CI -16.49, -8.28) and 2.54 (95% CI -1.49, 6.57) respectively (p=0.001). No significant differences in patient satisfaction or compliance were reported between the treatment and control groups.
CONCLUSIONS: The results of this study clearly demonstrate that pharmaceutical care improves drug therapy outcomes in hypertensive patients. Furthermore, the outcomes validate the benefits of pharmaceutical care clinics in managed-care environments, and the granting of prescribing privileges to clinical pharmacists.

311. Implementation and evaluation of a computerized sample medication dispensary (SMD) at a family medicine residency program (FMRP). *David M. Hachey, Pharm.D.,* Rex W. Force, Pharm.D., FCCP, BCPS, Wendy Force, R.Ph., Julie M. Johnson, Pharm.D., Melanie Sadler, Pharm.D.; Idaho State University, Pocatello, ID.

PURPOSE: We describe the implementation of a computerized SMD at a FMRP and report medical staff perceptions regarding this system.
METHODS: JCAHO regulations for sample medications at hospital outpatient clinics have become more stringent, requiring more precise record keeping. A secure, pharmacist-maintained SMD was developed at a FMRP to replace a system in which physicians and nurses maintained inventory. Prescriptions written by physicians were presented to and filled by pharmacists in a manner similar to retail pharmacy. Labeling and counseling fulfilled state law and OBRA '90 requirements. Pharmacists maintained a medication database (FileMaker Pro®) of samples and patient profiles and interacted with physicians at the point of care. Eight months after implementation of the new system, a survey was administered to physicians and nurses to evaluated their use and perceptions of the SMD.
RESULTS: Survey results of 30 physicians and nurses revealed they are more satisfied with the new SMD compared with the previous system (p<0.0001). Physicians did not think the system was burdensome and strongly agreed their patients benefited from interacting with pharmacists. Physicians believed they have written more prescriptions since implementation of the new system and utilized the knowledge of pharmacists more since the SMD has been open. Finally, it was determined that physicians frequently consider quantity of samples available when writing for samples and frequently consider samples when determining which drugs to use within a given medication class.
CONCLUSION: A successful computerized SMD has been established at a FMRP and was associated with high levels of physician and nurse satisfaction.

312. Implementation and assessment of a medication assistance program (MAP) at a family medicine residency program (FMRP). *James R. Sharp, Pharm.D. candidate,* David M. Hachey, Pharm.D.; Idaho State University, Pocatello, ID.

PURPOSE: To describe the implementation, financial impact, and provider perceptions of a MAP at a FMRP
METHODS: A MAP was established to assist uninsured patients with obtaining medications from pharmaceutical company programs (PCP). Physicians referred patients to a pharmacy intern who recorded demographics, income, and medication information. The intern applied for medications, logged their receipt, and distributed them to patients (typically a 3-month supply). Prescription data were processed over a 6-month period from these log sheets. The medication value was calculated from prices at www.drugstore.com (as of 6/1/2001). A six-question survey was administered to all physicians and nurses to evaluate perceptions of the MAP.
RESULTS: A total of 319 prescriptions were processed over 6 months for 160 patients valued at $74,746.30 ($234.31 per 3 month supply). Most frequently obtained medication classes were antidepressants (21%), diabetic agents (18%), and proton pump inhibitors (13%). Most frequently accessed programs were Bristol-Myers-Squibb (17%), Merck (15%), and AstraZeneca (14%). Physicians reported the MAP was greatly beneficial to their patients' overall health and quality of life. If patients did not have access to the MAP, physicians reported they would first use more affordable medication, then attempt to use sample medications chronically. Physicians and nurses also reported they would support the institution of a $5 fee per application processed.
CONCLUSIONS: A successful MAP has been established at a FMRP assisting 160 uninsured patients. This MAP obtained numerous medications from various PCP valued at $75,000. This MAP was also associated with a high degree of provider satisfaction.

313. Automatic IV to oral conversion program in a community hospital. *Patricia . Grunwald, Pharm.D., BCPS,* Bonnie Pitt, R.Ph., MAS; Frederick Memorial Healthcare System, Frederick, MD.

PURPOSE: The purpose of the program is to decrease risk of adverse events related to IV therapy and provide cost savings to the institution by changing from IV forms of medications to oral medications as soon as a clinical pharmacist assessment showed the patient could tolerate oral therapy.
METHODS: Doctor of Pharmacy trained clinical pharmacists who completed the institution's competency for IV to oral interchanges were given

prescriptive authority to switch selected IV medications to oral when the patient met criteria. The criteria were approved by the institution's Pharmacy and Therapeutics Committee before implementation. The interchanges were completed by 12 noon of each day and became effective at 9 AM the next morning to allow the patient's physician the opportunity to override the interchange. Clinical pharmacists followed up 48 hours later to assess the effectiveness of the interchange. Medications interchanged included: H2-blockers, digoxin, ciprofloxacin, fluconazole, levofloxacin, gatifloxacin, metronidazole, clindamycin, cefuroxime, cefazolin, azithromycin, metoclopramide, and trimethoprim/sulfamethoxazole. The analysis includes number of interchanged drugs, number of over-ridden interchanges, length of stay, percent of physicians who do not participate, and cost savings.
RESULTS: Less than 10% of interchanges were over-ridden. There were no cases of denied days or of patients discharged early. Medication costs were less in the patients who were changed to oral therapy. Length of stay assessment was not completed at the time of this writing.
CONCLUSIONS: Clinical pharmacists can provide IV to oral interchanges resulting in lower drug costs.

314. Establishment and evaluation of a refill protocol system (RPS) in a family medicine residency outpatient clinic (FMROC). *Melanie A. Sadler, Pharm.D.,* Rex W. Force, Pharm.D., FCCP, BCPS; Idaho State University, Pocatello, ID.

PURPOSE: Prior to August 1999 at our FMROC, medication refill requests (MRR) were processed by nurses. There was no systematic process ensuring necessary therapeutic monitoring with this procedure. Most recently, MRR were routed through a pharmacy intern who gathered pertinent data and contacted each physician in person or by telephone. This technique was time consuming, cumbersome, and involved numerous phone calls to providers. We describe subsequent development, implementation, and evaluation of a pharmacist-mediated RPS for chronic medications to enhance quality of care at this FMROC.
METHODS: A series of algorithm-style protocols were created for refill authorization of various chronic medications. These protocols contained specific requirements for disease state and/or medication-appropriate monitoring. A daily log of total number of MRR, those approved by protocol, and laboratory, procedure (pap, mammogram), and follow-up appointments recommended was maintained. After four months, a survey of physicians and nurses was conducted to evaluate overall satisfaction with the RPS.
RESULTS: Over four months, 1451 total MRR were received (17.5/day), 41% (n=588) of which were authorized, via the RPS, without contacting the provider. Also, 213 laboratory tests or procedures and 280 follow-up appointments were recommended by the RPS. Remaining MRR were referred to providers. Survey results indicated the FMROC staff were more satisfied ($p<0.00001$), thought patients received better monitoring ($p=0.0001$), and number of phone calls were reduced with the RPS than the previous method.
CONCLUSIONS: The RPS reduced phone calls and provider time involved with processing MRR for chronic medications. Staff at the FMROC expressed overall satisfaction and thought necessary therapeutic monitoring was improved with the RPS.

315. Safe and appropriate dofetilide therapy through a physician-pharmacist dose initiation program. *Krista A. Coval, Pharm.D.,* Shannon W. Finks, Pharm.D., BCPS, David Kuhl, Pharm.D., Mark A Coppess, M.D., Eric Johnson, M.D., FCCP; Baptist Memorial Hospital Memphis; Stern Cardiovascular Center, Memphis, TN.

PURPOSE: Initial administration of dofetilide requires patient hospitalization, continuous electrocardiographic (ECG) monitoring, dosing individualization, and drug interaction and contraindication screening. This program was developed to ensure safe and appropriate initiation of dofetilide therapy through a physician-pharmacist collaborative effort.
METHODS: A protocol was developed to initiate and manage dofetilide therapy. All patients admitted to Baptist Hospital for the initiation of dofetilide therapy automatically received a clinical pharmacy consult. The pharmacist screened the patient for drug and disease contraindications to dofetilide, potential drug interactions, and baseline renal function. An initial dofetilide dose is recommended based upon estimated creatinine clearance (determined using Cockcroft and Gault equation with actual body weight). Twelve-lead ECGs were obtained before the initial dose and three hours after every dose. Doses were adjusted when QT prolongation was noted. Prior to patient discharge, the pharmacist counseled the patient and assisted with paperwork necessary for the patient to receive outpatient therapy.
RESULTS: A total of 35 patients were initiated on dofetilide therapy from 11/00 to 6/01. Patients (n=3) with drug contraindications were not initiated until an appropriate washout period had elapsed. All patients received appropriate initial doses of dofetilide. Dosage reduction was required in 11 patients due to QT prolongation. Nine patients required drug discontinuation due to QT prolongation, treatment failure, and physician discretion (n=4, 4, and 1, respectively). All patients received medication education by the pharmacist prior to discharge.
CONCLUSION: The management of dofetilide by a physician-pharmacist team has ensured safe and appropriate drug initiation, avoidance of contraindications, appropriate monitoring, and facilitation of patient discharge from the hospital.

316. Evaluation of community pharmacies in Taipei. *Hsiang-Yin Chen, M.S., Pharm.D.,* Ming-Hui Liao, B.S., Wen-Chi Yang, B.S. candidate, Wuan-Jin Leu, B.S. candidate, Kuan-Yang Hsu, Ph.D.; Taipei Medical University; Taipei Municipal Wan-Fang Hospital, Taipei, Taiwan.

PURPOSE: Separation of pharmacy practice from medicine profession was implemented at 1997 in Taiwan. However, most patients still do not seek community pharmacists for prescription dispensing and medication consultation. Current study was designed to assess the difficulties of management community pharmacy in Taipei.
METHODS: A group of trained interviewers visited all the community pharmacies in Taipei City. The criteria to evaluate the equipment and environment of community pharmacy were developed and validated between interviewers. The criteria contained 14 ranked items with a perfect score of 22, including the displayed order of the OTC medication, design of dispensing room, number of medication counseling sheets available, professional demeanor of the pharmacist. The pharmacist in-charged was asked to fill a questionnaire to elaborate current situation of management, satisfaction to profit and foresight to future. Profit satisfaction was evaluated as 10-point scale and foresight as 5-point scale.
RESULTS: Total number of pharmacies surveyed was 137 with a complete rate of 82.5 %. Mean score graded by interviewers was 6.2 ± 4.6 and mean of profit satisfaction was 3.9 ± 2.09. Seventy percent of pharmacies provided less than 5 of medication counseling sheets. About half of the pharmacists (64 over 137, 46.7%) predicted future toward negative direction, and 25.5 % toward positive direction. Spearman rho coefficient was significantly correlated between interviewer's score and profit satisfaction.
CONCLUSIONS: Intervention to encourage and fortify the improvement in the equipment of environment of community pharmacies should be made immediately to meliorate the future of community pharmacy in Taipei City.

317. Implementation of criteria-based reimbursement strategy to facilitate billing of pharmaceutical care in the ambulatory care environment. *Susan Bear, Pharm.D.,* Stacy Martin, Pharm.D., Fern Paul-Aviles, M.S., R.Ph., Alissa Smith, Pharm.D., Roderick D. Teat, Pharm.D.; Carolinas HealthCare System, Charlotte, NC; Pfizer Inc., Research Triangle Park, NC.

The increased demand for health care services in the ambulatory care environment has resulted in lengthy delays for new patient appointments and follow up care. Implementation of Pharmaceutical Care Clinics in our ambulatory environment has created opportunity for pharmacists to serve as physician extenders resulting in more efficient utilization of physician office time as well as improved use of our pharmaceutical resources. Reimbursement while desirable was not possible due to lack of an existing system to document pharmaceutical care in our ambulatory care clinics. Using practice protocols created for each area of service and the "incident to" billing language from Medicare as a guide, complexity triggers were developed to objectively identify intensity and level of service. This strategy was translated into a form on the palm device utilizing Pendragon technology. This form will have the ability to track the following: patient demographics, type of clinic service, visit information including medical history, complexity of issues, new problems, medication related events, action and follow-up. As the pharmacist progresses through the form on the palm device, an ongoing summation of the "triggers" is being compiled to objectively identify the level of service to be billed. In addition to standardizing billing of pharmaceutical care, this data provides justification for new clinical pharmacy services, targets areas for improvement in patient care and identifies opportunities to optimize the entire medication use process. Data analysis will also provide cost avoidance dollars per pharmacist expense that can be compared to national benchmarks.

318. Pharmacist-managed practice model for ambulatory patients with asthma. *Tami L Remington, Pharm.D.,* Andrea Heaberlin, Pharm.D., Bruno DiGiovine, M.D., MPH; Henry Ford Health System, Detroit, MI.

PURPOSE: To provide patients the benefits of specialized care in a pharmacist-managed physician-supervised asthma clinic.
METHODS: Patients are enrolled into the asthma clinic through referrals from primary care providers or small group asthma education class, or by invitation based on disease control assessed using a validated questionnaire [Asthma Therapy Assessment Questionnaire (ATAQ)]. At the initial visit, spirometry, a medication assessment and complete medical evaluation are performed by the pharmacist and pulmonologist. The pharmacist, using a collaborative drug therapy agreement congruent with national and system guidelines, conducts the majority of subsequent follow-up care. The effectiveness of the clinic is assessed using financial, clinical and humanistic outcomes.
RESULTS: Sixty patients were enrolled into the clinic in the first year. The mean ATAQ scores were 2.20 ± 1.05 at baseline and 1.35 ± 1.06 and 1.00 ± 1.11 at six months and one year, respectively. There were three emergency room encounters and two hospitalizations six months prior to enrollment, and two ER encounters and one hospitalization during the subsequent twelve

months. Combined ER and hospital costs were $22,416 at baseline and $28,767 at one year. Medication costs were $408/patient/6 months at baseline, and $637/patient/6 months and $584/patient/6 months at six months and one year, respectively. At baseline, 45.7% of patients were on medium- or high-dose inhaled steroids. At six months and one year, 75% and 54.5% of patients were on medium- or high-dose inhaled steroids
CONCLUSION: A pharmacist-managed physician-supervised asthma clinic can improve patient outcomes.

319. A computer-aided learning program for case history taking: a validation of a case study form. *Anun Chaikoolvatana, B.Sc., Pharm.D.,* Larry Goodyer, B.Pharm., Ph.D.; King's College; University of London, London, UK.

PURPOSE: This study documented a computer-aided learning (CAL) for case history taking via a validation of case study form in order to 1) assess the quality of CAL program content based on pathological and therapeutics (usability), 2) assess the method of assessing CAL material, and 3) assess the quality of case history taking by comparing from three grades of pharmacists including: pre-registered, certificate, and senior pharmacists (sensitivity).
METHODS: Twenty-one hospital pharmacists were asked to complete the CAL program on diabetes case. Each pharmacist then filled out a standard report form based on information gain from the CAL program, which was marked according to a previously validated scoring system.
RESULTS: With regard to usability, pharmacists did not describe any difficulties using the case presentation form. With regard to sensitivity, twenty-one pharmacists were enrolled in this study. The overall results indicated that, as expected, the pre-registered pharmacists had significantly worse scores (59% ± SD 6.79) than the certificate (74% ± SD 4.69) $p<0.05$. Although the senior pharmacists (66% ± SD 8.76) a higher percentage than pre-registered pharmacists, this failed to reach significance. There was no statistically significantly different between senior and certificate pharmacists
CONCLUSION: The case presentation form was found to be both usable and reproducible in assessing case histories delivered through the CAL program. Whilst it is sensitive enough to distinguish between inexperienced and experienced pharmacists, it may be less sensitive in distinguishing between those with some further graduate training. The tool will now be used to compare CAL history taking to that taken from a real interview.

320E. Impact of pharmacist visits on heart failure patients receiving home care services. *Darren M. Triller, Pharm.D.,* Robert A. Hamilton, Pharm.D., Nancy M. Waite, Pharm.D., Laurie L. Briceland, Pharm.D.; Albany College of Pharmacy, Albany, NY.

PURPOSE: Heart failure (HF) is a major cause of morbidity and mortality, and hospital and clinic-based pharmacist interventions have improved clinical outcomes in these settings. To demonstrate the impact of clinical pharmacist visits on home care patients with HF, a prospective cohort study was performed.
METHODS: Twenty-one patients with HF referred to a home care agency consented to receive pharmacist visits in addition to standard nursing care for 60 days. The pharmacist performed comprehensive assessments, provided counseling, and communicated with other professionals. Quality of life, the primary outcome, was assessed at baseline and 60 days using the Minnesota Living with Heart Failure Questionnaire. Clinical pharmacist interventions were documented, categorized, and ranked according to level of actual or potential clinical significance by a multidisciplinary panel including a clinical pharmacist, an advanced practice nurse and a physician.
RESULTS: Patients were predominantly elderly (73.8 ± 13.6 years) and were prescribed large numbers of medications (10.1 ± 4.6). Quality of life scores improved significantly from baseline during the period ($p<0.05$). One hundred seventeen visits were performed (median 5 per patient) and 140 interventions were documented (median 6 per patient, range 0-15). Ten patients (47.6%) required hospitalization during the study period, 4 due to worsened heart failure (19.0%).
CONCLUSIONS: Home care patients with heart failure have a poor quality of life, are frequently hospitalized, and frequently experience drug-related problems. Pharmacists providing visits to home care patients with heart failure can effectively identify and resolve clinically relevant problems and improve patient quality of life.
Presented at the 20th Annual Meeting of the National Association for Home Care, Las Vegas, NV, October 16, 2001.

321. Effect of a pharmacist-managed diabetes clinic on hemoglobin A1c values and screening indices for diabetes management. *Mary Ann Halloran, Pharm.D.,* Robin R. Feuge, Pharm.D., Dea L. Brueggemeyer, R.Ph., Shirley R. Lockie, M.D.; University of Oklahoma, Oklahoma City, OK; Tinker Air Force Base, OK.

OBJECTIVE: To determine the impact of a diabetes management service (DMS) on adherence with key diabetes performance measurements and glycemic control in a United States Air Force medical treatment facility (MTF).
METHODS: A pharmacist-managed DMS was developed to screen, educate and manage diabetic patients in a military MTF. Referred patients received laboratory evaluation, intensive education and drug therapy management through DMS providers. Fasting lipid profiles (FLP), hemoglobin A1c (HbA1c), and microalbumin results were evaluated for concordance with accepted clinical practice guidelines in referred patients. The percent of diabetics receiving primary care in the MTF and attaining these same indices was also evaluated. Additionally, the change in HbA1c values was evaluated for DMS referred patients.
RESULTS: HbA1c values were obtained within the previous year for 100% of DMS patients compared to 76% of patients not referred. An FLP was obtained within the previous year for 99% of DMS patients and 73% of patients not referred. Microalbumin screening was performed for 90% of patients seen by DMS and 80% of patients not referred. Thirty referred patients were followed for a sufficient length of time to obtain a follow-up HbA1c. In these patients, the mean baseline HbA1c was 9.3% compared to 7.4% at follow-up (mean time between values was 3.7 months; $p<0.01$).
CONCLUSION: A focused diabetes management service can improve adherence to key indices for diabetes management. Additionally, marked improvement in HbA1c levels can be achieved in a relatively short period of time through intensive diabetes management and education.

322. A multidisciplinary approach to hypertension management: using pharmacists as education providers in a family medicine clinic. *Orly Carter, Pharm.D.,* Karen Gunning, Pharm.D.; University of Utah, Salt Lake City, UT.

PURPOSE: To evaluate whether pharmacists can improve hypertension outcomes and patient satisfaction when utilized as education providers in a primary care setting.
METHODS: Patients saw a pharmacist for 3 visits for education and blood pressure monitoring. Primary outcomes included hypertension control per JNC VI guidelines and changes in clinic blood pressure measurements. Secondary outcomes included degree of patient education, satisfaction with the pharmacist intervention, and type of antihypertensive agents used. Patient education was measured by a multiple-choice survey. Patient satisfaction was measured using a validated survey, with items rated on a five-point Likert scale. Statistical analysis included the Fisher's Exact test for nominal data and the Student's t-test (paired) for continuous data.
RESULTS: At study conclusion 3 out of 13 patients were controlled per JNC VI guidelines, with 2 additional patients controlled within 1-2 mm Hg. Mean blood pressure measurements decreased from 155/86 to 147/84. Significant improvements occurred in clinic systolic blood pressure measurements ($p<0.05$), but not diastolic measurements. Education scores improved from 86% to 93% ($p<0.03$), and patient satisfaction scores improved from 75% to 97% ($p<0.03$). Clinic providers accepted 83% of the medication recommendations made by the pharmacist. The use of diuretics more than doubled by study conclusion compared to baseline.
CONCLUSIONS: Pharmacists can serve as education providers to patients about hypertension, and patients are receptive to a pharmacist's involvement in their care. Utilizing a pharmacist as part of a multidisciplinary team improves blood pressure control and patient satisfaction in a primary care setting. Longer follow up time is required to achieve blood pressure goals per JNC VI guidelines.

323. Development and evaluation of a statewide program to increase medication access for indigent solid-organ transplant patients. *Marie A. Chisholm, Pharm.D.,* Bridgett D. Kendrick, C.Ph.T., Charlene Garrett, Diane Glenn, Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: Many solid-organ transplant patients (SOT) have inadequate prescription insurance coverage and do not have the financial resources to pay for all of their medication needs. In recognition of this, many pharmaceutical manufacturers make medications available free or at reduced costs to eligible patients who do not have access to essential medications by any other means. In order to educate healthcare professionals and to assist patients enroll in medication assistance programs, the Medication Access Program (MAP) was developed.
METHODS: The MAP office has five employees, including two pharmacists. Georgia's SOT patients in need of medication assistance or their healthcare professionals contact MAP concerning the availability of assistance programs. MAP instructs patients and healthcare personnel on the application process required by the pharmaceutical companies and serves as a liaison between the patient, physician, and the pharmaceutical companies. Program personnel records the number of patients served and the average wholesale price (AWP) of medications supplied through the program. Patients who used MAP's services as of January 1999 were asked to complete a patient satisfaction survey.
RESULTS: From October 1999 to June 2001, MAP has assisted over 180 SOT patients enroll in medication assistance programs, accounting for approximately $1.6 million (AWP cost) of medications. Approximately 48% of the $1.6 million represents immunosuppressant medications, the other 52% mostly represents that of cardiovascular, antimicrobial, and gastrointestinal medications. Patients (n=125) had a mean score of 93.4 ± 9.8 (highest achievable survey score is 100) on the satisfaction survey indicating that MAP provided a valuable service to them.
CONCLUSION: The MAP was successful in helping needy solid-organ

transplant patients obtain medications and patients are pleased with the services provided.

324. Outcomes of proactive pharmacist interventions in the co-management of oral contraceptive (OC) and hormonal replacement therapy (HRT) patients. *Linh K. Vuong, Pharm.D.,* Ronald J. Ruggiero, Pharm.D., Clifton Louie, R.Ph., D.P.A., Nancy Milliken, M.D.; University of California at San Francisco, San Francisco, CA.

PURPOSE: To determine if proactive telephone interventions and access to a clinical pharmacist can increase OC/HRT adherence and improve patient satisfaction with care. Furthermore, the study aims to show the cost effectiveness of having a clinical pharmacist manage patients on OC/HRT.
METHODS: Ongoing, prospective, randomized-controlled study. Patients are recruited and randomly assigned to an intervention or non-intervention group. Intervention patients receive two phone calls from the pharmacist during the three-month study period. Patients in both groups are required to keep a three-month calendar of the time they take their medications.
RESULTS: 42/90 (46.7%) patients enrolled completed the study, 24 dropped-out for various reasons, 24 are ongoing. In the intervention group (IG), 9/15 (60%) versus 10/27 (37%) in the non-intervention group (NIG) did not miss any pill during the three-month period, (p=0.20). In addition, patients in the IG reported that pharmacists were more accessible than other providers (physicians [MDs], nurse practitioners [NPs]; p<0.05). Pharmacists were rated higher in the IG vs in the NIG as a helpful source of information about OC/HRT, (p=0.05). Furthermore, patients were more satisfied with pharmacist's care compared to other providers', (p=0.09). On average, the study pharmacist saved 23.6 minutes of MD/NP time per patient.
CONCLUSION: Our modest sample size and results do not allow for a definitive conclusion of whether intervention phone calls by the pharmacist will increase patient's adherence to OC/HRT. However, the results do suggest that pharmacists are equally as effective, if not more than, other providers in managing patients on OC/HRT.

325. A drug and breastfeeding consult service for a state department of health's women, infant and children program. *David S. Ziska, Pharm.D.*; The University of Mississippi; University of Mississippi Medical Center, Jackson, MS.

This presentation will familiarize its audience with a novel practice involving a clinical pharmacist as a consultant to lactation consultants employed by the Mississippi State Department of Health Women Infant and Children (WIC) breastfeeding program. The Mississippi WIC program serves approximately 100,000 women and children. Many WIC clients that were breastfeeding required prescription and OTC medications to maintain health and lactation consultants found physician knowledge on drug and breastfeeding safety incomplete. In 1998 a need was identified for expert consultation services to lactation consultants working for the Mississippi WIC breastfeeding program. Subsequently, faculty at the University of Mississippi Medical Center were contacted and a faculty member with interest and expertise was identified. The service was conceived as a voluntary service for the purpose of providing evidence-based evaluation of medication and breastfeeding safety for WIC clients. Evidence provided includes information from the drug manufacturer and primary and tertiary literature. Expertise is sought when a lactation consultant identifies a client that is breastfeeding and either needs to initiate drug therapy or is already receiving one or more medications. Once the consultation is initiated detailed information about the nursing dyad is obtained. The pharmacist then analyzes each situation and provides a recommendation and supporting evidence either verbally or electronically. Physicians are also contacted and the recommendation is discussed directly with the pharmacist if they do not accept the information provided through the lactation consultant. Given that many infants are prematurely weaned unnecessarily because of drug therapy, demand for this service has expanded.

STUDENT, RESIDENT, FELLOW RESEARCH IN PROGRESS

These papers describe original research by students, residents, and fellows in therapeutics, pharmacokinetics, pharmacodynamics, pharmacoeconomics, and pharmacoepidemiology in which the research effort is still on-going. The abstract title and authors are published in *Pharmacotherapy*; the full abstract will be published in the meeting program book.

326E. Effects of diltiazem on the pharmacokinetics and pharmacodynamics of methylprednisolone in healthy volunteers. *Brent M. Booker, Pharm.D.,* Mindy H. Magee, Pharm.D., Robert A. Blum, Pharm.D., Christian D. Lates, M.D., William J. Jusko, Ph.D.; University at Buffalo the State University of New York; Kaleida Health, Buffalo, NY.

PURPOSE: To study the effects of diltiazem (Dilt) on the pharmacokinetics (PK) and pharmacodynamics (PD) of methylprednisolone (MP).
METHODS: Five healthy males received a single IV dose of MP (0.3 mg/kg) on day 1; 180 mg oral dose of SR Dilt daily on days 3-7; and both drugs concomitantly on day 8. Plasma MP concentrations were assayed by HPLC and assessed by compartmental fitting using WinNonlin. PD response-time profiles for plasma cortisol concentrations (by HPLC) and CD4, CD8 lymphocyte cell counts (by FACS and hemocytometry) were evaluated by basic and extended indirect response models using ADAPT II.
RESULTS: The mean (± SD) parameter estimates are (*p<0.05):

	$T_{1/2}$ (hr)*	CL (L/hr)*	Cortisol IC_{50} (ng/ml)	CD4 IC_{50} (ng/ml)	CD8 IC_{50} (ng/ml)
MP	2.28 ± 0.37	25.2 ± 4.84	0.45 ± 0.44	9.2 ± 3.4	18.5 ± 11.8
MP+Dilt	3.12 ± 0.40	16.8 ± 2.1	0.78 ± 0.77	10.7 ± 2.9	20.9 ± 14.9

CONCLUSIONS: Dilt decreased MP CL by ~33%, resulting in a longer $T_{1/2}$ and greater exposure of MP shown by a higher AUC in all five men. However no adrenal suppression or lymphocyte trafficking pharmacodynamic interaction seem to occur between the two compounds in healthy male subjects. Support: NIH Grant No. 24211
Presented at the 102nd Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Orlando, FL, March 6-10, 2001.

327. Preventable adverse drug events in hospital: medications, types of errors, and outcomes. *Penkarn Kanjanarat, M.S.,* Almut Winterstein, Ph.D., Richard Segal, Ph.D., Randy Hatton, Pharm.D., Ricardo Gonzalez-Rothi, M.D., Thomas Johns, Pharm.D.; University of Florida; Shands Hospital, Gainesville, FL.

PURPOSE: To explore the nature of preventable adverse drug events (pADEs) in hospitals as described by I) medication causing adverse outcomes, II) type of error, and III) adverse outcome. Identified high-priority areas will be used to develop computerized screens for pADE detection and prevention.
METHODS: Literature search of MEDLINE (1966-May 2001), IPA (1970-Mar 2001), and hand search. The search was limited to peer-reviewed literature reporting pADE incidence in hospitalized patients and frequencies of at least one pADE descriptor (I-III).
RESULTS: 12 studies published between 1994-2001 reported pADE incidences ranging from 0.16-16.2%. Cardiovascular drugs were responsible for the largest proportion of pADE, mean 17.2% (4.3-27.0), followed by antiinfectives 13.8% (3.3-42.1%), analgesics/opioids 11.1% (6.3-28.6%), psychoactive drugs 10.8% (1.3-30.8%), and anticoagulants 8.2% (4.3-20.0%). The most common adverse outcomes were gastrointestinal problems (2.6-32.1%), hematological problems and bleeding (9.0-45.0%), central nervous (5.0-32.1%), cardiovascular disorders (7.5-17.0%), and allergic reactions (2.5-50.0%). Most pADEs occurred in the prescribing stage and were dose-related, followed by administering, dispensing and transcribing. Frequently reported examples of pADEs included digoxin overdose associated with bradycardia, antiinfectives prescribed despite history of allergy, warfarin overdose resulting in hemorrhage, opioid over- or underdose associated with poor pain control or respiratory depression.
CONCLUSIONS: The highlighted pADEs identify well-known problems in pharmacotherapy. Even though pADEs have been described as highly heterogeneous, our analysis suggests that a small number constitutes a substantial proportion of pADEs, and that targeting these priority areas could significantly reduce overall pADE incidence.

328. Analysis of a pharmacist-managed hypertension service on blood pressure control and medication adherence in an indigent ambulatory population. *Stephanie H. Mok, Pharm.D.,* Ruth E. Emptage, Pharm.D., Martin R. Giannamore, Pharm.D., Laura E. Hall, Pharm.D., James D. Nash, Pharm.D.; Ohio State University, Columbus, OH; Pfizer, Inc., Columbus, OH.

PURPOSE: To determine whether blood pressure control and medication adherence in hypertensive patients can be improved by a pharmacist-managed hypertension service in an indigent, ambulatory population.
METHODS: Patients were referred by physicians and nurses to pharmacists practicing within The Columbus Neighborhood Health Center system between February and July 2001. The inclusion criteria were ≥18 years of age and a diagnosis of primary hypertension. Exclusion criteria were as follows: 1) a diagnosis of secondary hypertension, 2) seen by a pharmacist for hypertension management for ≥ 6 months in the past, and 3) current illicit drug use. On the initial visit, the pharmacist established BP goals (according to JNC VI), performed a medication history, and provided patient education. Blood pressure (BP), weight, and pulse were measured at baseline and subsequent pharmacist visits (≤ 1 month intervals). Medication adherence was assessed using a validated questionnaire at the initial and final visits.
RESULTS: Fourteen patients were enrolled. Data from eight patients are currently available for interim analysis. The average baseline and final BPs were 147.4/87.9 and 134.0/76.9 mm Hg, respectively. Five patients (62%) reached JNC VI goal BP. The average time for patients to reach their BP goal was 25 days. The average reduction in systolic and diastolic BPs were 13.4 and 10.9 mm Hg, respectively. Twenty-five percent of patients had a dosage change in their antihypertensive medications and thirteen percent had an addition of another antihypertensive drug. Twenty-five percent had both a dosage change and addition of another antihypertensive drug. The final assessment on patients' medication adherence is pending.
CONCLUSIONS: Pharmacists can improve blood pressure control in an ambulatory setting with focused efforts on patient education and disease management. The final analysis of this pilot project will be utilized to

determine if implementation of a pharmacist-managed hypertension clinic would be effective in this system.

329. Effectiveness of a pharmacist-based smoking cessation program and impact on patient's quality of life. *Alan J. Zillich, Pharm.D.,* Melody Ryan, Pharm.D., BCPS, CGP, Aimee Adams, Pharm.D.; University of Kentucky Chandler Medical Center, Lexington, KY.

PURPOSE: Pharmacists have demonstrated their impact on managing several chronic disease states, but data concerning their impact on smoking cessation is lacking. The goal of this study is to evaluate the effectiveness of a pharmacist-based comprehensive smoking cessation program. Smoking has been shown to have a negative impact on health-related quality of life. However, no studies have examined the effect of smoking cessation on quality of life (QOL). A secondary goal of this study was to measure QOL throughout a smoking cessation attempt.
METHODS: Patients were self-referred into a comprehensive smoking cessation program. The program utilized weekly, one-hour, group sessions over 12 weeks. The program incorporated nicotine replacement therapy with extensive behavioral modification counseling. Trained pharmacists served as program facilitators. Smoking cessation was chemically verified at 3 and 6 months via exhaled carbon monoxide. QOL was measured using the smoking cessation QOL questionnaire at baseline, 2 weeks, 1 month, 2 months, 3 months, and 6 months.
RESULTS: Twenty-five patients have been enrolled. Chemically verified abstinence rates at 3 and 6 months were 48.0% and 16.7% respectively. QOL improved from baseline to 6 months across all health domains. Additional data collection is ongoing and will be presented.
CONCLUSION: The pharmacist-based smoking cessation was moderately effective and demonstrated a positive impact on patient's QOL.

330. Low-density lipoprotein goal attainment of patients with diabetes and/or coronary heart disease in a community-based primary care medical group. *Dawn C. Fuke, Pharm.D.,* Jacquelyn S. Hunt, Pharm.D., Joseph Siemienczuk, M.D., Michael W. Estoup, Pharm.D., Daniel R. Touchette, Pharm.D., M.A.; Oregon State University; Providence Medical Group, Portland, OR.

PURPOSE: Diabetic (DM) patients have a cardiac event risk comparable to patients with coronary heart disease (CHD). Currently, there are few studies evaluating LDL goal attainment in the community-based primary care setting, and no studies in DM patients. The purpose of this study was to determine the proportion of DM and/or CHD patients meeting target LDL ≤ 100 mg/dl in a community-based primary care setting.
METHODS: Retrospective cross-sectional study that identified patients with DM and/or CHD via electronic medical record search of pertinent problem list codes, a medication in the antidiabetic or nitrate class, or HbA1C ≥ 7.0% (3/97 – 3/01). Patient demographics, last LDL-level, and use of lipid-lowering agents were also analyzed.
RESULTS: The study identified 12,289 patients (5771 DM-only, 5040 CHD-only, and 1478 with DM and CHD). DM patients with co-existing CHD attained LDL target most often (DM 17.4%, CHD 22.7%, DM+CHD 30.4%, p<0.001). Furthermore, they were more likely to have a LDL level drawn within the past year (DM 38.4%, CHD 37.3%, DM+CHD 45.3%, p<0.001). When patients were treated with lipid lowering agents, DM patients with CHD were more likely to be treated to goal (DM 32.3%, DM+CHD 40.8%, p=0.001). Multivariate logistic regression analysis revealed that disease state (DM+CHD), but not age or sex was associated with LDL goal attainment.
CONCLUSION: Although achievement of LDL goal is poor in the individual states of diabetes and CHD, the combined diseases improve the likelihood of LDL goal attainment. Identification of barriers is necessary to improve the delivery of known beneficial interventions in these high-risk population.

331. Methods for estimating creatinine clearance in critically ill patients. *Mandy M. Walker, Pharm.D.,* Allison R. Browning, Pharm.D., Elizabeth Landrum Michalets, Pharm.D., BCPS, Gilbert W. Gleim, Ph.D.; Mission St. Joseph's Health System, Asheville, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC.

PURPOSE: This study evaluated the precision of various Cockcroft-Gault (C-G) equation derivatives for estimating creatinine clearance (CrCl) in comparison to measured 24-hour creatinine clearance (ml/min) in critically ill patients.
METHODS: Variants of the C-G equation were (1) using total body weight (2) using weights typical of clinical practice (PBW) and (3) using PBW plus adjustment of Scr up to 1.0 mg/dl in patients >75 years. CrCl was measured in 24 adult ICU patients with stable renal function (<25% change in Scr over 2 days). Patients were 60.2 ± 3.8 years old and weighed 78.4 ± 3.5 kg (mean ± SEM).
RESULTS: The mean measured 24 hour urine CrCl was 102.9 ± 10.5 ml/min. The table depicts the explained variance (r^2), the p-value, the mean ± SEM, and the significance of the paired t-test with actual CrCl.

C-G Estimate	r^2	p	Mean ± SEM	Paired t-test	% error
1	0.706	<.001	109.7 ± 11.2	0.115	+ 6.8%
2	0.767	<.001	96.1 ± 9.7	0.198	-6.8%
3	0.682	<.001	89.3 ± 10.5	0.035	-13.6%

Equation 2 was the most precise and equation 3 was the least precise, significantly underestimating CrCl. Equation 2 can more precisely predict CrCl using the equation: $CrCl = 0.947\ (C\text{-}G_{PBW}) + 11.82$. Using aminoglycosides as a clinical indicator, dosing was different 37.5% of the time.
CONCLUSION: C-G CrCl estimation using the weight typical of clinical practice provides the highest degree of correlation with 24-hour urine CrCl in critically ill patients. Adjustment of Scr to 1.0 mg/dl in the elderly decreases precision.

332. Retrospective study on common ambulatory used antibiotics and warfarin interaction. *Tracy Veronen, Pharm.D. candidate,* Yun Lu, Pharm.D., M.S., BCPS, Katie Won, Pharm.D.; University of Minnesota; Hennepin County Medical Center, Minneapolis, MN.

PURPOSE: This study is used to determine the severity of common ambulatory used antibiotics (amoxicillin, Augmentin, azithromycin, ciprofloxacin and co-trimoxazole) and warfarin interaction.
METHOD: By retrospective reviewing of Hennepin County Medical Center Anticoagulation Clinic patients charts (total of 300) between June 1997 to December 2000, all INR readings were analyzed from the first day to 28th day after the addition of the studied antibiotics.
RESULTS: After the addition of amoxicillin, four out of 54 (7.6%) INR readings were supratherapeutic. There were 5 our of 35 (14%) INR readings were elevated after the addition of Augmentin, of which two INR >5. While for azithromycin, there were 6 out of 42 (14.3%) INR readings were supratherapeutic after the initiation of azithromycin started. On the other hand, twenty-seven supratherapeutic INR were reported out of 45 (60%) patient's visits after the addition of ciprofloxacin. After the addition of co-trimoxazole, four supratherapeutic INR were reported out of 28 (14%) patient visits. Of all the above INR elevation, no acute bleeding episode was reported, nor acute reversion of anticoagulation was required.
CONCLUSIONS: Higher incidence of ciprofloxacin and warfarin interaction was observed at HCMC anticoagulation clinic. Close INR monitoring is necessary for the first two weeks after the addition of the above study drugs with the addition precautions for concurrent ciprofloxacin and warfarin therapy.

333. Gross examination of the rat placenta and fetal liver following *in utero* exposure of nelfinavir. *Sarah K. Wymer,* Cheryl A. Lieb, Eunsun Cho, Pharm.D., Cliff M. Monahan, DVM, Ph.D., Patty Fan-Havard, Pharm.D.; Ohio State University, Columbus, OH.

PURPOSE: Hyperglycemia is associated with HIV-1 protease inhibitors (PI). An increase in placental weight and a decrease in fetal liver weight have been reported in rat model of diabetic pregnancies. This study investigated placenta and fetal liver changes in pregnant rats treated with nelfinavir (NFV).
METHODS: Sixteen female rats were randomly assigned to control or NFV-treated (100 mg/kg/day) groups. Rats were mated overnight once weekly. Sperm-positive vaginal smears denoted day 0 of gestation. Necropsy was performed on day 20. The uterus was removed and immersed in PBS. The placentas and fetuses were isolated, weighed and measured. Fetal livers were removed and weighed immediately. Non-fasting glucose and insulin levels were analyzed from maternal serum.
RESULTS: Four control litters (55 fetuses) and five NFV-treated litters (73 fetuses) were analyzed. Placental area was significantly larger in the NFV-treated group compared to controls, 1.52 ± 0.015 cm^2 vs 1.45 ± 0.020 cm^2, (p=0.0025). Mean placental weight was higher in NFV-treated (0.58 ± 0.007 g) than controls (0.46 ± 0.006 g); p<0.001. No difference was noted for fetal weight or size between groups; however, a significantly lower fetal liver to fetus weight ratio was observed in the NFV-treated group, 0.081 ± 0.002 vs 0.097 ± 0.002, (p<0.001). Maternal non-fasting glucose was not different between groups. Maternal insulin levels are pending
CONCLUSION: Preliminary data demonstrate differences in placental weight and size, and fetal liver size, which are consistent with the model of diabetic pregnancies despite a lack of difference in maternal non-fasting glucose levels.
Supported by AFPE grant.

334E. Pharmacodynamic response surface analysis of combination antibiotic regimens against *Staphylococcus aureus*. *Brent M. Booker, Pharm.D.,* Alan Forrest, Pharm.D., L. Stahl, B. Botzer, Patrick F. Smith, Pharm.D.; University at Buffalo; Roswell Park Cancer Institute, Buffalo, NY.

PURPOSE: Our objective was to evaluate combinations of V, L, rifampin (R), and clindamycin (C), which shares a binding site in close proximity to L, against clinical isolates of *Staphylococcus aureus* (SA), using a pharmacodynamic (PD) response surface approach.
METHODS: MICs of 2 clinical isolates (MSSA and MRSA) from neutropenic cancer patients with bacteremia were determined according to NCCLS macrobroth dilution techniques. Initial screening for interaction between V, L, R and C was performed by checkerboard panels, followed by traditional time-kill studies with between sub to 10x MIC concentrations. In each case, the growth control, each drug alone and the combination data were co-modeled (fit simultaneously) using nonlinear regression (SAS version 8.1) and a Hill

type PD response surface model. Area under the growth curve, normalized for control, was used as a measure of drug activity. Akaike's Information Criterion was used to discriminate between interaction models.
RESULTS: The MRSA and MSSA strains yielded V, L, R and C MICs of 1, 4, 0.001, 0.25 and 1, 8, 0.008, 0.5 mg/ml respectively. FIC values for V/C, and L/C combinations demonstrated antagonism (FIC>4). The PD surface analysis revealed combinations of V/C to be antagonistic, L/C additive and L/R additive with some regions of synergy. The PD model fit the data well, throughout the entire surface.
CONCLUSIONS: PD response surface analysis incorporates all available data and is useful for evaluating in vitro activity of antibiotic combinations. V and C were antagonistic against both strains of SA evaluated, while L/C was not. V/R and L/R showed low-level synergy.
Presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Chicago, IL, September 22-25, 2001.

335. Incidence of cytomegalovirus viremia in heart transplant recipients during the intravenous ganciclovir shortage. *Nina M. Naeger, Pharm.D.,* Jennifer K. Long, Pharm.D., BCPS, Morton P. Goldman, FCCP, BCPS, Pharm.D., Robin K. Avery, M.D.; The Cleveland Clinic Foundation, Cleveland, OH.

PURPOSE: This study determined the incidence of cytomegalovirus (CMV) viremia in heart transplant recipients receiving alternative means of CMV prophylaxis during the intravenous (IV) ganciclovir shortage. Secondary objectives were to review the incidence of allograft rejection, number of patients treated for CMV viremia, and to differentiate those with viremia into CMV syndrome, CMV disease, or CMV infection.
METHODS: A retrospective review of all patients undergoing heart transplantation at The Cleveland Clinic Foundation (CCF) between April 1, 1999 and September 30, 2000 was conducted. Data was extracted from the patient chart, CCF Heart Transplant Database, Phamis® Last Word Orders/Results System, and Megasource® Pharmacy Database. CMV viremia was defined as any detectable viral load.
RESULTS: Ninety patients underwent heart transplantation during the review. Seventy-one percent of patients received the traditional CCF IV ganciclovir prophylactic regimen (CCF-IVGCV), and the remaining 29% received an alternative regimen (AR). The most common AR utilized oral ganciclovir. The overall incidence of viremia was 46% in CCF-IVGCV versus 50% in AR. All 70 patients developed allograft rejection. Eighty-three percent of patients in CCF-IVGCV were treated at least once for CMV viremia versus 90% in AR. Differentiation of patients with viremia into CMV syndrome, disease, or infection is in progress.
CONCLUSION: The ARs used during the shortage seem to be equivalent to CCF-IVGCV in preventing CMV viremia in our heart transplant recipients. Additionally, the incidence of allograft rejection and the number of patients treated for CMV viremia appear comparable between the two groups.

336. Evaluation of a clinical practice guideline for fluconazole early presumptive therapy using a fungal risk assessment index. *Joni L. Fukami, B.S.Pharm., Pharm.D.,* Roger L. White, Pharm.D., FCCP, E. Douglas Norcross, M.D., Cathy Worrall, B.S.N., R.N., Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: A risk assessment index (RAI) and practice guideline for fluconazole early presumptive therapy (EPT) was developed at our institution (1998). Results of a retrospective medication use evaluation (1999) indicated that the guideline was not being fully utilized. The aim of this study is 1) to assess the predictive value of the RAI using a score ≥40 as the threshold for receiving EPT, and 2) to assess fungal outcomes in fluconazole treated patients.
METHODS: The clinical validity of the RAI will be assessed in surgical patients undergoing open abdominal procedures (approximately 200 patients) by calculating the positive and negative predictive values in patients who do not receive fluconazole EPT. Fungal outcomes, defined as the presence or absence of a systemic fungal infection in patients treated with fluconazole EPT, will be assessed using Chi squared.
RESULTS: To date, 53 patients (28 male, 25 female) have been evaluated. The median age is 53 years (21-85 years). The median length of stay is 10 days (3-71 days). Thirty four of the 53 patients (64%) had RAI scores <0 and did not receive fluconazole therapy. As predicted by the RAI, 32 (94%) did not develop a systemic fungal infection. Fourteen of the 53 patients (26%) received fluconazole. Of these, eight (57%) had RAI scores ≥40. One of these developed *Candida albicans* fungemia and expired.
CONCLUSIONS: Final results of the RAI assessment and analysis of fungal outcomes in patients who received fluconazole EPT will be presented.

337. Assessment of vancomycin susceptibility and incidence of tolerance in staphylococci after a decade of selective pressure. *Raymond Cha, Pharm.D.,* Jane B. Wells, Pharm.D., George P. Allen, Pharm.D., Peggy S. McKinnon, Pharm.D., Michael J. Rybak, Pharm.D., FCCP.; Wayne State University; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: The emergence of vancomycin-intermediate staphylococci and increased prevalence of treatment failures over the past decade prompted us to investigate the impact of 10 years of vancomycin utilization on susceptibility and the development of tolerant isolates.
METHODS: 200 *Staphylococcus aureus* and coagulase-negative staphylococci blood isolates, including patients with endocarditis, were obtained from Detroit Receiving Hospital, a level-1 trauma center. 50 *Staphylococcus aureus* isolates, 25 from 1987-1993 and 25 from 2000-2001, were obtained for preliminary analysis. Minimum bactericidal concentrations (MBC) and minimum inhibitory concentrations (MIC) for vancomycin were performed according to the National Committee for Clinical Laboratory Standards. Time-kill analyses were performed for selected isolates with MBC:MIC ratios of ≥ 4 µg/ml. Vancomycin tolerance was defined as an MBC:MIC ratio of ≥ 32 or a ≤ 90% kill after 6 hours.
RESULTS: The MICs for early isolates ranged from 0.5 to 2.0 µg/ml (median 1.0 µg/ml) while MBC:MIC ranged from 1 to 8 (median 2). MICs for recent isolates ranged from 0.125 to 2.0 µg/ml (median 1.0 µg/ml) while MBC:MIC ranged from 1 to 16 (median 2). Susceptibility results and MBC:MIC ratios did not differ statistically between the two periods (p>0.05). MBC:MIC ratios and time-kill analyses on selected organisms revealed no vancomycin-tolerant isolates.
CONCLUSION: Currently, no appreciable alteration in susceptibility for the tested portion of *S. aureus* was noted. Although there were some isolates in the recent portion that exhibited MBCs as high as 16, this was not statistically significant at this time. Additionally, no intermediate-resistant or tolerant isolates were identified over the evaluation period. Until the entire pool has been analyzed, no conclusive statements can be made. Further evaluation of the remaining isolates will be presented. Potential changes in vancomycin susceptibility trends are important and research in this area is currently ongoing in our lab.

338. Preliminary results of abrupt cessation of total parenteral nutrition in patients with abdominal surgery. *Yu-Hsuan Yen, M.S.,* Hsiang-Yin Chen, Pharm.D., Shing-Mei Hsu-Lee, R.Ph., Mao-Chih Hsieh, M.D.; Taipei Municipal Wan-Fang Hospital; Taipei Medical University, Taipei, Taiwan.

PURPOSE: Abrupt cessation of total parenteral nutrition (TPN) is not recommended by current guidelines due to the fear of hypoglycemia. Slow tapering may not be cost-effective in patients without risk factors of hypoglycemia. Patients received abdominal surgeries with unintentionally abrupt cessation of TPN were retrospectively evaluated.
METHODS: Ten patients with abrupt cessation (AC) of TPN were compared with 15 patients having tapering cessation (TC) of TPN. The rates of infusion in TC patients were gradually tapered over 8 hours before complete discontinuation. Glucose levels during the first 4 hours after cessation, a symptomatic hypoglycemic score and vital signs were collected from nursing and progress note.
RESULTS: Mean level of glucose decreased from 137 ± 52 (baseline) to 115 ± 36 mg/dl after discontinuation of TPN in TC group, compared with 151 ± 32 to 113 ± 35 mg/dl in AC group. No significant difference between groups was found in the change of glucose levels before and after TPN cessation. No case in AC group developed severe hypoglycemia (glucose concentration <45 mg/dl). There were also no significant differences in symptomatic score of hypoglycemia, systolic and diastolic blood pressure, and pulse between two groups.
CONCLUSIONS: The preliminary results demonstrated that the patients received abdominal surgeries who were abruptly stopped TPN did not develop symptomatic hypoglycemia. Further studies are needed to compare the effects of different tapering regimens of TPN in the patients without risk factors.

339. Using the complete blood count to assess the potential interaction between dexamethasone and chemotherapeutic agents. *Jeffrey J. Mucksavage, Pharm.D.,* Mark C. Geraci, Pharm.D., Linda R. Bressler, Pharm.D., Lingtak-Neander Chan, Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Dexamethasone, a commonly used anti-emetic agent and cytochrome P450 3A4 inducer, may affect the pharmacokinetics of some anti-cancer agents modulating drug-related toxicities. This study intended to compare inter-cycle complete blood counts (CBCs) to determine whether drug-related toxicity associated with an anthracycline-based regimen is associated with this drug interaction.
METHODS: Medical records of non-Hodgkin's lymphoma patients treated with CHOP between 1985 and March 2001 at the Oncology Care Center at the University of Illinois were reviewed. Patients were separated into two groups based on whether or not dexamethasone was administered during chemotherapy. Body surface area (BSA), age, concurrent medications, demographics, and CBCs were documented. The inter-cycle CBCs were compared.
RESULTS: Out of approximately 900 profiles reviewed, 37 patients who fulfilled the inclusion criteria were identified of which 17 are currently analyzed. The average age in the dexamethasone group is 46 years with an average BSA of 1.87 m^2 compared to the non-dexamethasone group of 58 years and 1.74 m^2. In terms of white blood cell count (WBC), the average percent of recovery of the leukocytes between the start of cycle 1 and the start

of cycle 2 is 105% in the non-dexamethasone group and 92% in the dexamethasone group. Complete results including analysis of the remaining patients, inter-cycle comparisons, and effects on platelets will be presented at the meeting in October.
CONCLUSIONS: Our interim analysis suggests that inter-cycle comparisons of WBCs may not be the most sensitive means to detect an interaction between dexamethasone and CHOP. A prospective trial evaluating CBC nadirs or other pharmacodynamic parameters should be investigated to characterize this drug interaction.

340E. Adverse drug reaction reporting in the oncology setting: development and implementation of guidelines. *Wendy Jiang, Pharm.D.,* Lisa Anselmo, Pharm.D., George Carro, R.Ph., M.S., BCOP; Kellogg Cancer Center, Evanston Hospital, Evanston, IL.

PURPOSE: There are many undesired yet expected adverse drug reactions (ADRs) with chemotherapy. An example is chemotherapy-induced diarrhea resulting in admission to the hospital for hydration and reduction of next treatment dose. The value of reporting these ADRs is debatable. The first objective of this project is to describe current practices of ADR reporting in the oncology setting. The second objective is to develop ADR reporting guidelines for chemotherapy in our institution.
METHODS: A survey was sent to cancer centers in the Eastern Cooperative Oncology Group and to ACCP Oncology/Hematology members. We also performed a literature search for discussions on this topic. Finally, we developed specific guidelines for ADR reporting with chemotherapy.
RESULTS: Pharmacists from eighteen cancer centers responded to the survey. Eighty three percent of the pharmacists claimed to use the ASHP definition for reporting ADRs with chemotherapy. Fifty six percent of the respondents believe ADR reporting with chemotherapy should be the same as that with other medications. When presented with scenarios satisfying the ASHP ADR definition, over 90% of the pharmacists report that these would not be reported as ADRs.
CONCLUSIONS: There appears to be a lack of consensus on chemotherapy-related ADR reporting. Although pharmacists in our study claimed to follow the ASHP ADR reporting definition, most of the scenarios satisfying that definition, would not be reported. This may be due to pharmacists viewing chemotherapy-related ADRs as inevitable side effects instead opportunities for development of prevention strategies. To address this issue, we developed guidelines for reporting ADRs with chemotherapy.
Presented at the Great Lakes Pharmacy Residency Conference, Madison, WI, April 21, 2001.

341. A variation of Rogers' adoption of innovation model characterizes accrual of breast cancer patients into clinical trials. *Shannon L. Coonce, Pharm.D.,* William R. Doucette, Ph.D.; University of Iowa, Iowa City, IA.

PURPOSE: Patient accrual into oncology clinical trials is low with less than 3% of all oncology patients enrolling in a clinical trial. This low accrual rate affects the ability of a drug to be studied effectively. The objective of this project was to determine if a variation of Rogers' Adoption of Innovation Model using communication methods, physician practice type and practice setting variables characterized physician accrual of breast cancer patients into clinical trials.
METHODS: A multiple regression analysis was performed using SPSS version 10.0 on survey data obtained from 247 oncologists out of 1196 for an overall response rate of 21%. Usable data for the regression were available for 138 cases.
RESULTS: The overall regression model was significant ($p<0.01$), with r^2 0.406. Five variables were significantly associated with the number of breast cancer patients enrolled in clinical trials. The five significant ($p<0.05$) variables were: number of interactions with other oncologists in the past 6 months, use of continuing education classes as a source of cancer regimen information (negatively correlated), amount of time spent working with organizations to introduce new cancer therapies into the community, percentage of patients with strong preference for their treatment decisions, and number of oncologists in the practice.
CONCLUSION: These findings suggest patients' confidence in their treatment decision can influence their participation in a clinical trial. Also, encouraging oncologists to interact with each other and working to introduce new cancer regimens can increase clinical trial enrollment.

342. Implementing and evaluating a community pharmacy quality assurance program. *Reda Al-Houssayni, Pharm.D.,* Jeff Goad, Pharm.D., BCPS, Kathy Johnson, Pharm.D., Ph.D., Mike Rudolph, Pharm.D.; University of Southern California, Los Angeles, CA ,

PURPOSE: To establish a community pharmacy based quality assurance program (QAP), document provider and pharmacy errors, analyze data provided by error reports, create a forum for pharmacist peer discussion of errors, and design appropriate error interventions for quality improvement.
DESIGN: a retrospective analysis of medication errors based on reported data through a form.
METHODS: Policy and procedures were developed for the QAP that included community pharmacy setting from chain, academia, and independent practice. Pharmacists were then educated on need for a QAP and trained on the documentation form. Pharmacy and prescriber errors were documented over a 4 months period using a standard medication error documentation form created for this program. Data collected on errors include patient age and sex, refill or new prescription, prescription details, number of prescriptions concurrently dispensed, error descriptor, error location in the prescribing and dispensing process, personnel committing the error, standard error category for potential to cause patient harm, and quality improvement recommendation. All data on errors will be held confidential, considered non-discoverable and used anonymously for peer evaluation when appropriate.
RESULTS: 243 reports were received. 87 (32 %) errors were attributable to prescriber errors while 183 (68 %) errors occurred at the pharmacy. 99 (41%) of errors were committed by pharmacy technicians, 63 (26 %) by prescribers, and 40 (17 %) by pharmacists. 170 (70%) of errors were discovered by pharmacists, 31 (13 %) by patients, and 26 (11%) by technicians and clerks. 210 (87 %) of errors did not reach the patient, 26 (11%) of medication errors reached the patient but caused no harm, and 2 (1%) of errors reached the patient, caused no harm, but the patient required monitoring.
CONCLUSION: medication errors in the community pharmacy setting represent a serious hazard to sound drug therapy. Implementing and evaluating a quality assurance program can filter out both prescriber and pharmacy errors.

343. The safety and tolerability of prolonged propofol sedation of critically ill, mechanically ventilated infants and children. *Allison M. Chung, Pharm.D.,* Todd A. Kociancic, Pharm.D., Lia H. Lowrie, M.D., Jeffrey L. Blumer, Ph.D., M.D., Michael D. Reed, Pharm.D.; Case Western Reserve University; Rainbow Babies and Children's Hospital, Cleveland, OH.

INTRODUCTION: Propofol is widely used as a sedative to facilitate mechanical ventilation in adults and children, despite repeat warnings regarding possible propofol -associated, serious adverse effects in pediatric patients.
PURPOSE: To determine the safety of prolonged propofol sedation in critically ill, mechanically ventilated pediatric patients.
METHODS: The medical records of all patients admitted to our pediatric intensive care unit (PICU) who received propofol between 1992 and 1999 were reviewed. 1500 patients were identified; to date, 146 have been evaluated identifying 84 patients who received propofol sedation for > 6 hours. The patient's history, in-hospital course, complete propofol dose and administration schedule, concomitant sedative / drug therapy, vital signs and comprehensive laboratory analysis were documented.
RESULTS: The 84 patients (38% F) ranged in age from 0-17 years (mean 2.75 years) with the majority receiving propofol as monotherapy. The drug was infused at a median dose of 6.8 mg/kg/hour for 7-144 hours (median 42 hours). Preliminary inspection of patient clinical course and laboratory data reveled no specific abnormalities related to propofol administration. Overall, the drug appeared to be safe and no patients developed any metabolic abnormalities associated with propofol administration.
CONCLUSION: This preliminary assessment suggests propofol is a safe sedative in the PICU. It is very likely that data collection and analysis will be completed by the time of the date of presentation.

344. Pharmacokinetics (PK) of perifosine, an oral alkylphosphocholine signal transduction modulator, in a phase I trial with different loading and maintenance schedules in patients with refractory neoplasm. *Waverly E. Woo, Pharm.D., Ph.D.,* Richard A. Messmann, M.D., Donna Headlee, R.N., Susan G. Arbuck, M.D., Edward A. Sausville, M.D., Ph.D., William D. Figg, Pharm.D., FCCP; National Cancer Institute, NIH, Bethesda, MD.

PURPOSE: Perifosine, an alkylphosphocholine signal transduction modulator, is currently in phase I clinical trial at the NCI. The objective of this study was to determine the maximum tolerated dose (MTD) of perifosine and to characterize the PK profile from the phase I clinical trial.
METHOD: Various loading (on day 1) and maintenance doses (on days 2-21) of perifosine were orally administered daily to patients with refractory neoplasm on a 28-day cycle including a 7-day break. Dose levels, as loading/maintenance doses, tested to date were: 300/50 (dose level I), 600/100 (dose level II), 900/150 (dose level III), 1200/200 (dose level IV), 1500/250 mg (dose level V) for the first cycle; 100/50, 200/100, 300/150, 400/200, 1000/250 mg for all subsequent cycles, respectively. Time points for pharmacokinetic sampling were: pre-treatment, 24, 48, and 72-hr post-loading dose for cycle 1; pre-loading dose, days 15 and 21 prior to daily maintenance dose for all cycles. Perifosine concentrations in patient plasma, determined by a LC/MS assay, were fitted to a one-compartment PK model using ADAPT II.
RESULTS/CONCLUSION: A total of 9 patients, three patients per dose level from dose levels I-III, were evaluated for PK. The results showed linearity between dose and day-21 peak concentration. The mean ± SD PK parameters were: $T_{1/2}$ 151.3 ± 41.3 hr, apparent total clearance 1.173 ± 0.196 L/hr, and apparent volume of distribution 257.9 ± 88.6 L. At evaluated dose levels I-III, the observed peak perifosine plasma concentrations on day 21 were comparable to those predicted from the previous phase I study with single weekly dosing. Within 48 hr after the loading dose, approximately 70% of

day-21 peak concentration was achieved. Drug accumulation between cycles was minimal at all of the tested dose levels despite the long half-life and large volume of distribution of perifosine. MTD has not been reached. Dose escalation and patient accrual are ongoing.

345. A trough-only vancomycin monitoring program at a university teaching hospital. *Laurel S. Fields, Pharm.D., M.S., BCOP,* Joseph S. Bubalo, Pharm.D., BCOP, BCPS, Daniel R. Touchette, Pharm.D., M.A., Karen B. Farmer; Oregon State University at Portland; Oregon Health & Science University, Portland, OR.

PURPOSE: Vancomycin monitoring standards vary widely in the literature and at Oregon Health & Sciences University (OHSU). Objectives were to 1) evaluate the effectiveness of a formalized vancomycin trough-only monitoring program against current practice and 2) evaluate program safety, therapeutic, and pharmacoeconomic outcomes.
METHODS: Clinical pharmacists prospectively recommended trough-only vancomycin levels and monitored patients using a standardized dosing and monitoring tool. This intervention group was compared to a historical control. Medical history, initial vancomycin regimen and monitoring parameters, vancomycin rationale, age, serum creatinine, concurrent nephrotoxic medications, and in-hospital course were recorded. Interventions, physician acceptance, vancomycin therapeutic outcomes, and safety data were evaluated.
RESULTS: Ninety-eight trough-only and 135 control patients were enrolled from several wards, including BMT, ICU, and internal medicine. Demographic data were not different between the groups. The trough-only program was equally effective compared with the control group. An average 2.3 vs 3.3 total serum concentrations ($p<0.001$) and 0.4 vs 1.3 peak concentrations were drawn per patient respectively ($p<0.001$). Time from the first dose to the first vancomycin concentration was 2 vs 1.5 days ($p<0.001$). Physicians accepted 97% of the interventions. The trough-only program averaged $271/patient vs $307/control patient. No nephrotoxicity was attributable solely to vancomycin. The trough-only monitoring program resulted in equivalent outcomes; detailed analysis will be presented.
CONCLUSIONS: A trough-only vancomycin monitoring program resulted in statistically fewer vancomycin levels without affecting either safety or therapeutic outcomes throughout the adult hospital population. This program offers equally effective vancomycin monitoring with fewer laboratory draws, increased pharmacist involvement, and institutional savings.

346. Pharmacist-initiated osteoporosis screening: comparing the impact of direct and indirect pharmacist-physician communication. *Ashley D. Butler, Pharm.D.,* Tricia M. Berry, Pharm.D., Megan N. Lavin, Pharm.D.; St. Louis College of Pharmacy, St. Louis, MO.

PURPOSE: To determine the efficacy of pharmacist-initiated osteoporosis screening programs, this study 1) assessed the effect of screening on implementation of patient-specific prevention/treatment, and 2) determined the impact of post-screening direct pharmacist-physician communication on patient management.
METHODS: Screening of women ≥ 45 years old was conducted at community sites (e.g., senior centers, churches) and at a chain pharmacy. All subjects provided informed consent and completed a medical/dietary history questionnaire. T-scores were obtained using a Lunar Achilles Express bone ultrasonometer. Individuals were evaluated for osteoporosis risk factors and educated about risk factor modification. Post-screening reports: 1) chain pharmacy screening results were reported for each subject with a T-score < -1.0 via a letter mailed directly to her physician (direct report); 2) community screening results were reported in a letter given to each subject to deliver to her physician (indirect report). Post-screening phone follow-up with each subject is in-progress to determine initiation of prevention/treatment.
RESULTS: A total of 537 subjects were screened (275 chain, 262 community) between December 2000 and April 2001; 309 patients (58%) were at moderate-to-high risk of developing osteoporosis (140 chain, 169 community). Post-screening data collection will be completed by September 2001.
IMPLICATIONS: Pharmacist-initiated osteoporosis screening can identify a significant number of patients at moderate-high risk of developing disease in both community and chain pharmacy settings. The effects of screening on implementation of prevention and treatment will be reported. In addition, the impact of direct vs indirect post-screening communication with physicians will be compared.

347. Preliminary analysis of the drug utilization information collected in the Australian Schizophrenia Care and Assessment Program (SCAP). study. *Yvonne Czyz, Pharm.D. candidate,* Jessica Goren, Pharm.D., Bill Montgomery, B.Pharm., Judith Barr, Sc.D.; Eli Lilly, West Ryde, NSW, Australia; Northeastern University, Boston, MA.

PURPOSE: To develop an analytic plan for interpreting the drug utilization data collected by the SCAP study and to evaluate a method for predicting the likely therapeutic impact of each course of drug therapy using the Defined Daily Dose (DDD) as a proxy for the therapeutic dose.
METHODS: Comprehensive drug utilization data were collected for the first 150 patients during their first six months in the study. Each course of drug therapy was then plotted in Microsoft Project. via the following systems: the Pharmaceutical Benefits Scheme (PBS – the national pharmaceutical reimbursement authority, which captures all reimbursed prescriptions); directly from the patients medical records, and from the Hospital Pharmacy dispensary computer system. This data was merged to patients in the SCAP. We then compared the reference DDD for each drug from the first 150 patientscourse of therapy with thea proportion of the DDD dispensed to each patient over this period (calcDDD).
RESULTS: Of the 483 medication entries reviewed for the first 150 patients, 145 were excluded due to incomplete data. Out of the remaining 338 medication entries, 102 (30%) had a value greater than 50% of the reference DDD (i.e., these patients received at least half of the therapeutic dose over this period). When the reference range was expanded to 50-200% of the standard DDD, 86 (25%) medications were within this range. Therefore, approximately half of all drugs received by patients over this period were prescribed at doses likely to be associated with a therapeutic effect.
CONCLUSION: This approach has provided valuable insight into the complexities of analyzing longitudinal drug utilization data. A number of limitations of the existing data set were identified and considerable progress has been made towards developing a process to weight each course of therapy with its likely therapeutic impact. This data implies possible prescribing practices which would potentially be targeted to improve outcomes.

348. Evaluation of a patient and family education program for children and adolescents with attention deficit hyperactivity disorder. *Jennifer L. Baumgartner, Pharm.D.,* M. Lynn Crismon, Pharm.D., Molly Lopez, Ph.D.; University of Texas at Austin; Texas Department of Mental Health and Mental Retardation, Austin, TX.

PURPOSE: To determine the effects of a patient and family education program (PFEP) on outcomes in children and adolescents treated in community mental health clinics, specifically examining effects on knowledge, symptoms, functioning, adherence, and satisfaction.
METHODS: Subjects between ages 4-17 years, 11 months receiving psychiatric services for Attention Deficit Hyperactivity Disorder with or without comorbidities were eligible. Consenting patients/families were assigned to PFEP or treatment as usual (τ) based upon clinic from which services are received. Subjects are followed over six months with assessments at baseline, 3-month midpoint, and 6-month endpoint. Outcome measures include: pre/post knowledge test, Clinical Global Impression (CGI), Conners' Parent Rating Scale (CPRS-R:L), Conners' Teacher Global Index (CGI-T), Youth Outcome Questionnaire (YOQ), patient/family satisfaction survey, and adherence measures (refill/visit records and verbal report).
RESULTS: Twenty-eight patients are enrolled in PFEP and 20 patients in τ. The mean age of the sample is 10.4 years and consists of predominantly Caucasian (60%) males (79%) with psychiatric comorbidities (69%). At baseline, the sample tended to be moderately ill (mean CGI 3.8) with significant hyperactivity, impulsivity and oppositionality based on mean CPRS-R:L T-scores of 76.8, 73.0, and 70.2, respectively. No significant differences between groups exist regarding age, race, gender, CGI, CPRS-R:L, or CGI-T. Study completion is estimated to be September 2001.
CONCLUSIONS: Literature is lacking regarding education programs for children with psychiatric disorders. Being a population particularly at risk for suboptimal outcomes, this study will provide information as to a specific intervention for improving treatment adherence and patient outcomes.

349. Hospital costs associated with bone marrow transplant patients by cancer. *Walter G. Scott, Pharm.D.,* David C. Wordell, B.S., Andrew A. Howe, Pharm.D., Gene A. Gibson, Pharm.D.; Hospital of the University of Pennsylvania, Philadelphia, PA; Grady Health System, Atlanta, GA.

PURPOSE: Current healthcare trends are toward lower reimbursement and rising costs across all areas of hospital care. Limited data is available in terms of drug resource utilization necessary to treat specific cancers in bone marrow transplant (BMT) patients. This study describes the demographic characteristics and drug resource utilization associated with the following cancers and BMT: acute and chronic myelogenous leukemia (AML and CML), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and breast cancer.
METHODS: We created a Structured-Query-Language (SQL) database comprised of multiple tables that reflected key aspects of patients' hospital stay. A retrospective database analysis was conducted using SQL to obtain descriptive statistics of our BMT patients for fiscal year FY 2000 and the first half of FY 2001.
RESULTS: A total of 219 patients were evaluated, 165 (75.3%) diagnosed with the above-mentioned cancers. Preliminary data includes cancer type, number of patients (n), percent (%) of BMT drug cost, and 95% confidence interval: NHL (n=53, %=24.0, CI 14.5, 33.5), CML (n=23, %=17.1, CI 12.6, 21.5), AML (n=24, %=14.5, CI 14.4, 14.6), breast (n=18, %=14.2, CI 13.0, 15.4), MM (n=47, %=9.2, CI 7.4, 11.0). Classes of drugs most frequently administered as a percentage of total BMT drug cost were chemotherapy (28.6%), colony stimulating factors (24.3%), antibiotics (13.9%), intravenous immune globulin (8.7%), anti-emetics (6.6%), and immunosuppressants (6.6%).

CONCLUSION: This data may be employed for budget projections, benchmarking of BMT programs, investigation of drug use, and exploration of outcomes associated with drug utilization. Additional data will be presented.

350. The efficacy of oral ganciclovir in prophylaxis of cytomegalovirus in liver transplant recipients. *Cassandra J. Carwise, Pharm.D.,* Drew Silverman, Pharm.D.; Florida A&M University; Tampa General Hospital, Tampa, FL.

PURPOSE: Prevention of cytomegalovirus (CMV) disease with an effective prophylactic regimen will decrease the morbidity and mortality in orthotopic liver transplant recipients. Limited data supports the use of oral ganciclovir as and effective prophylactic agent for this patient population. We reviewed our practice to determine the effectiveness of oral ganciclovir in preventing CMV in patients following liver transplantation.
METHODS: Medical records of 130 patients that received a liver transplant between December 1996 to July 2000 were reviewed. Demographic information and risk factors for the development of CMV were extracted from the medical records and documented. The patients received intravenous ganciclovir 5 mg/kg every 12 hours post-transplant and converted to oral ganciclovir 1000 mg three times daily when oral medications were tolerable for a total of 90 days of therapy. CMV Immune Globulin was given to seronegative recipients who received a liver from a seropositive donor per protocol.
RESULTS: CMV disease developed in 5/130 (3.8%) and 1/130 (0.8%) developed CMV infection. In the high risk group of seronegative recipients of seropositive donors, 4/23 (17%) developed CMV disease. Only 1 (0.2%) of the 6 patients that developed CMV disease or infection received antibodies to lymphocytes.
CONCLUSION: Oral ganciclovir is an effective prophylactic regimen in preventing CMV in patients following liver transplantation. Before the availability of oral ganciclovir, oral acyclovir was the gold standard in preventing CMV in this patient population. Clinical trials have demonstrated the effectiveness of both medications and supports prophylactic therapy with intravenous ganciclovir followed by oral ganciclovir in liver transplant recipients.

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.

351. Aventis Oncology Fellowship: Folylpolyglutamate and hydrolase activity in acute lymphocytic leukemia blasts. William E. Evans, Pharm.D., FCCP, BCPS, *Amelia Wall, Pharm.D.*; St. Jude Children's Research Hospital, Memphis, TN.

Folylpolyglutamate hydrolase (FPGH) is a lysosomal enzyme responsible for the degradation of natural folate polyglutamates within the cell. It has also been shown that this enzyme hydrolizes (inactivates) methotrexate polyglutamates, which increases the potential for the drug to efflux out of the cell, thereby decreasing its activity. Data documenting activity of this enzyme has been obtained by other investigators in total cell lysates, but has never been investigated in subcellular compartments of primary leukemia cells. Because FPGH is primarily localized in the lysosomes, and the activity of FPGH is optimal at the lysosomal pH of 4.5 (versus cytosolic pH of 7.4), activity of FPGH measured in total cell lysate may not be meaningful. It is of interest from a drug resistance perspective whether the lysosomal activity of FPGH (the hydrolase of interest for methotrexate metabolism) is different in biological subtypes of ALL lymphoblasts.
Our hypothesis is that lysosomal FPGH activity is higher in T lymphoblasts compared to B-lineage lymphoblasts. A second hypothesis is that FPGH activity is higher in nonhyperdiploid B-lineage ALL than hyperdiploid B-lineage ALL. These hypotheses were tested both in vitro and in vivo in our laboratory.
We tested 5 human leukemia cell lines, including 3 T lineage leukemia cell lines (P12, CEM, and Molt4) and 2 B lineage cell lines (697 and Nalm6). The T lineage cell lines exhibited higher lysosomal GGH activity than Nalm6 cells (CEM 8.86 pmol/µg protein/hour, P12 13.87 pmol/µg protein/hour , Molt4 6.42 pmol/µg protein/hour, Nalm6 8.74 pmol/µg protein/hour) but the B lineage 697 cells exhibited highest activity (15.17 pmol/µg protein/hour) and faster metabolism of methotrexate polyglutamates over time. Next, leukemia blasts from 51 patients enrolled on the SJCRH ALL treatment protocol Total 15 were analyzed for GGH activity (9 = T lineage ALL and 44 =B lineage ALL, 3 of whom have hyperdiploid ALL). We have determined that a wide range of GGH activity exists among primary leukemia cells from patients, and in human leukemia cell lines of different lineage. These studies are ongoing to determine whether there are significant differences in GGH activity in total cell lysates, intact lysosomes and opened lysosomes in ALL blasts from patients with different lineage and genetic subtypes of ALL, and whether this translates to significant differences in the intracellular accumulation of MTC-PG in patients.

352. Ortho-McNeil Infectious Diseases Fellowship: Evaluation of the effect of varying fluoroquinolone dosing regimens on the mutant prevention concentration for *Staphylococcus aureus and Streptococcus pneumoniae* in an in vitro model of infection. *George P. Allen,* Glenn W. Kaatz, Joseph M. Blondeau, Michael J. Rybak; Wayne State University, Detroit, MI; J.D. Dingell Veteran's Affairs Medical Center, Detroit, MI; Royal University Hospital, Saskatoon, SK, Canada.

BACKGROUND: The mutant prevention concentration (MPC) is a novel method for characterization of antimicrobial potency, and may have utility as a pharmacodynamic parameter. MPC is defined as the MIC of the most resistant first-step mutant of a heterogeneous bacterial population, or the lowest antimicrobial concentration preventing growth of resistant mutants. Unlike traditional susceptibility testing, MPC is measured using a high inoculum likely to contain resistant subpopulations. We compared MPC values of fluoroquinolones against SA and SP, and studied the effect of MPC-derived concentrations of fluoroquinolones using an in-vitro pharmacodynamic model.
METHODS: MPCs were determined by plating ~10e9-10 colony-forming units (CFU) on fluoroquinolone-impregnated agar and measuring the lowest concentration inhibiting growth. An IVPM with infected fibrin clots was inoculated with SA or SP (~10e9-10 CFU/gm). Concentrations 2x-, 1/4x-MPC, and therapeutic troughs were targeted. Bacterial density was determined over 48h.
RESULTS:

	MIC/MPC (mg/L)				
Isolate	Moxifloxacin (MXF)	Ciprofloxacin (CIP)	Gatifloxacin (GAT)	Gemifloxacin (GEM)	Levofloxacin (LEV)
MRSA-494	0.06/0.125	0.125/1	0.06/0.125	0.015/0.06	0.125/0.5
SP-18	0.094/2	-	-	-	0.38/64
SP-42	0.094/1	-	-	-	0.5/32
SP-64	0.125/2	-	-	-	0.5/8
SP-74	0.094/16	-	-	-	0.38/8
SP-79	0.125/0.5	0.5/8	0.25/1	0.03/0.125	1/4

For therapeutic regimens versus MRSA-494, MXF, GAT, and GEM caused no resistance, while MIC elevations occurred with CIP and LEV. Supra-MPC regimens resulted in resistance for CIP only, while sub-MPC regimens caused MIC elevations for all agents. MXF caused no resistance in SP, while therapeutic LEV induced MIC elevations in 4 of 5 SP. T<MPC, Peak/MPC, and AUC/MPC were not predictive of resistance development.
CONCLUSIONS: For MRSA, resistance occurred more readily with CIP and LEV. MIC increases were more likely to occur with agents with higher MPCs. In SP, MXF produced no resistance, while therapeutic LEV caused 2-3 fold MIC increases in 4 strains. Higher MPCs were also associated with a greater likelihood for susceptibility changes. Of interest, the relationship between T>MPC and resistance development was not consistent for SP. Further evaluation of a range of MPC-targeted concentrations in various microorganisms may determine the MPCs utility as a pharmacodynamic tool.
Keywords: mutant prevention concentration, fluoroquinolone, resistance.

353. Ortho-McNeil Infectious Diseases Fellowship: Steady-state pharmacokinetics and urine elimination of indinavir alone and when combined with ritonavir in HIV-infected subjects. *Peter L. Anderson, Pharm.D.,* Richard C. Brundage, Pharm.D., Ph.D., Lane Bushman, B.S., Heather E. Wynn, Pharm.D., Courtney V. Fletcher, Pharm.D.; University of Minnesota, Minneapolis, MN.

PURPOSE: Urolithiasis is a recognized IDV complication occurring in ~9% patients/year. IDV is a substrate for P-glycoprotein, which lines proximal tubules and secretes substrates into urine. IDV's unbound renal clearance (CLr) is >3-fold higher than GFR, consistent with tubular secretion. We hypothesized RTV, a known inhibitor of P-gp, inhibits IDV CLr. Our objective was to compare the plasma pharmacokinetics and CLr of IDV during 800 mg Q8h versus 800/200 mg Q12h IDV/RTV combination therapy.
METHODS: 10 patients on standard IDV plus dual-nucleoside therapy for ≥12 weeks participated. Plasma and urine samples were collected over 8 hours for IDV therapy, and duplicated over 12 hours 3 weeks after initiation of IDV/RTV co-therapy. Noncompartmental analyses were used to characterize IDV plasma pharmacokinetics and CLr. Comparisons were made with a paired t-test following log transformation.
RESULTS: Data are median (range). RTV reduced the plasma IDV CL/F from 47 (21.7-233) to 18 (10.8-28.1) L/h, (p=0.0004) and increased the half-life from 1.1 to 3.1 hrs (p<0.0001). RTV increased IDV Cmax from 7.9 (2.1-14.6) to 9.9 (6.9-14.8) µg/mL (p=0.04) and Cmin from 0.12 (0.05-0.25) to 0.92 (0.61-2.1) µg/mL (p<0.0001). IDV CLr was 6.9 (4-15.4) before and 5.8 (2.9-17.1) L/hr after RTV therapy (p=0.29). Two patients experienced a 56 and 62% decrease in CLr.
CONCLUSIONS: RTV reduced the CL/F of IDV by 2.6 fold, but overall IDV CLr was unchanged. Two subjects experienced substantial reductions in CLr, which suggests some patients may be susceptible to RTV-associated inhibition of IDV CLr. Supported by: NIH MO1 RR00400 and RO1 AI 33835.

354. Wyeth-Ayerst Psychopharmacology Fellowship: Studies of olanzapine and clinical effects. *Heidi L. Liston, Pharm.D.,* John S. Markowitz, Pharm.D., David W. Boulton, Ph.D., C. Lindsay DeVane, Pharm.D.; Medical University

of South Carolina, Charleston, SC.

PURPOSE: Utilization of the atypical antipsychotic drugs continues to expand at a rapid pace. Despite their use in millions of patients, gaps exist in our understanding of their pharmacokinetics and dynamics. We sought to address this need with studies aimed at examining the potential drug interactions and the relationship between plasma concentration and clinical effects with olanzapine (OLZ).
METHODS: In preparation for studies in humans, an HPLC assay using ultraviolet detection for OLZ in human plasma and urine was developed. The limit of detection was 1 ng/ml. In study one, the hypothesis was tested that probenecid, as a general glucuronidation inhibitor, would impair the disposition of olanzapine administered to healthy volunteers. Twelve subjects (aged 22-42 years) received a single dose of OLZ 5 mg on two occasions, with and without the co-administration of probenecid. Multiple timed blood and urine samples were collected for 48 hours. In study two (in progress), inpatients treated for various psychotic conditions with OLZ donated a single blood sample at the outset of their therapy and under steady-state conditions for assessment of the relationship between plasma drug concentration and clinical effects as measured by the Brief Psychiatric Rating Scale.
RESULTS/CONCLUSIONS: In study one, drug clearance and elimination half-life were not significantly different between treatments; however, with probenecid the maximum OLZ concentration in plasma following a single dose, the area under the concentration versus time curve for 24 hours, and the absorption rate were all increased ($p<0.05$). These results suggest that some co-administered drugs commonly used in the initial treatment of psychotic patients with OLZ (i.e., valproate, lorazepam) may perturb the dose:concentration relationship of OLZ through inhibition of phase II metabolism. In actual patients, preliminary data analysis of study two failed to find a significant relationship between concentration and effect, although therapeutic drug monitoring for OLZ has been proposed as clinically useful. Further examination of factors which determine the disposition of OLZ may clarify which are important for influencing therapeutic outcome.

355. Wyeth-Ayerst Psychopharmacology Fellowship: Evaluation of a patient and family education program for children and adolescents with attention deficit hyperactivity disorder. *Jennifer L. Baumgartner, Pharm.D.,* M. Lynn Crismon, Pharm.D., Molly Lopez, Ph.D.; University of Texas at Austin; Texas Department of Mental Health and Mental Retardation, Austin, TX.

PURPOSE: To determine the effects of a patient and family education program (PFEP) on outcomes in children and adolescents treated in community mental health clinics, specifically examining effects on knowledge, symptoms, functioning, adherence, and satisfaction.
METHODS: Subjects between ages 4-17 years, 11 months receiving psychiatric services for attention deficit hyperactivity disorder with or without comorbidities were eligible. Consenting patients/families were assigned to PFEP or treatment as usual (τ) based upon clinic from which services are received. Subjects are followed over six months with assessments at baseline, 3-month midpoint, and 6-month endpoint. Outcome measures include: pre/post knowledge test, Clinical Global Impression (CGI), Conners' Parent Rating Scale (CPRS-R:L), Conners' Teacher Global Index (CGI-T), Youth Outcome Questionnaire (YOQ), patient/family satisfaction survey, and adherence measures (refill/visit records and verbal report).
RESULTS: Twenty-eight patients are enrolled in PFEP and 20 patients in τ. The mean age of the sample is 10.4 years and consists of predominantly Caucasian (60%) males (79%) with psychiatric comorbidities (69%). At baseline, the sample tended to be moderately ill (mean CGI 3.8) with significant hyperactivity, impulsivity and oppositionality based on mean CPRS-R:L T-scores of 76.8, 73.0, and 70.2, respectively. No significant differences between groups exist regarding age, race, gender, CGI, CPRS-R:L, or CGI-T. Study completion is estimated to be September 2001.
CONCLUSIONS: Literature is lacking regarding education programs for children with psychiatric disorders. Being a population particularly at risk for suboptimal outcomes, this study will provide information as to a specific intervention for improving treatment adherence and patient outcomes.

356. ACCP Pharmacotherapy Research Award: Effects of acute and chronic dosing of St. John's wort on cytochromes P450 enzyme activity in healthy volunteers. *Stanley W. Carson, Pharm.D.,* Christina E. Hill-Zabala, Pharm.D., Sheri L. Hoyler, Pharm.D., Michael Kotlyar, Pharm.D., Reginald Frye, Pharm.D., Ph.D., Michael Golding, M.D.; University of North Carolina, Chapel Hill, NC; University of Minnesota, Minneapolis, MN; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: The herbal product, St. John's wort (SJW), has received much attention in the last year for its potential to induce cytochrome P450 (CYP) 3A4 biotransformation. In contrast, in vitro studies suggest multiple CYP isoforms are inhibited acutely. We tested the hypothesis that SJW would inhibit CYP activity acutely and induce CYP activity upon chronic SJW administration in healthy volunteers.
METHODS: This was an open-label study of 6 men and 6 women. CYP activity was assessed using a probe-substrate cocktail consisting of: caffeine-CYP1A2; mephenytoin-CYP2C19; dextromethorphan-CYP2D6; chlorzoxazone-CYP2E1; and erythromycin breath test (ERBT)-CYP3A4. Intravenous ERBT was administered first with all other probes given orally one hour later. Blood was sampled 4 and 8 hours, and urine collected for 8 hours following cocktail administration. Subjects were studied at baseline, and then on day 1 (acute) and day 15 (chronic) of SJW administration (600 mg TID, *Kira*®).
RESULTS: CYP3A4 enzyme activity, as measured by the ERBT, significantly increased 1.2-fold ($p=0.007$) with acute dosing of SJW and 1.6-fold ($p=0.000003$) with 14 days chronic dosing. All subjects were CYP2D6 extensive metabolizers. Mean ratios for metabolic activity from baseline to day 1 and baseline to day 15 were not significantly different for the remaining four CYP enzymes: CYP1A2=1.01 and 1.06; CYP2C19=1.07 and 1.05; CYP 2D6=1.01 and 1.04; and CYP2E1=0.99 and 0.99, respectively.
CONCLUSIONS: Chronic dosing of SJW (*Kira*®) at 600 mg TID significantly induced CYP3A4 but not CYP 1A2, 2C19, 2D6, or 2E1 metabolic activity. There was no evidence for inhibition of any isozyme studied by either acute or chronic SJW administration.

357. Amgen Biotechnology Research Award: Diphtheria fusion toxin therapy in children with acute myeloid leukemia (AML) is feasible despite previous diphtheria toxin. *Philip D. Hall, Pharm.D.,* Bassem Razzouk, M.D., Tony E. Willoughby, Pharm.D., Thomas McClean, M.D., Arthur E. Frankel, M.D.; Medical University of South Carolina, Charleston, SC; St. Jude's Children Hospital, Memphis, TN; Wake Forest University, Winston-Salem, NC.

Although the prognosis of children with AML has improved over the past 20 years, many children still eventually die from relapsed or refractory disease. As a novel approach for the treatment of childhood AML, we are developing a novel fusion toxin (DT-GM) consisting of the catalytic and translocation subunits of diphtheria toxin (DT) linked to human granulocyte-macrophage colony stimulating factor (GM).
PURPOSE: A critical step in the development of DT-GM for use in children with AML involves assessing the ability of preformed anti-diphtheria antibodies to neutralize DT-GM. The purpose of this study was to determine if children with AML have pre-existing antibodies to DT-GM due to childhood immunizations against DTo.
METHODS: Sera from 33 children with AML (32 newly diagnosed, 1 relapse) and one with MDS have been collected. All scheduled DTo vaccinations were up-to-date except for the one child with MDS who was diagnosed at 4 months of age. Antibody neutralization capacity was assessed via an in vitro bioassay to inhibit DT-GM utilizing HL60 cells. Anti-DT-GM antibody concentrations were assessed by an enzyme immunoassay (EIA).
RESULTS: The median age of the 34 children is 11.8 years (range 4 months to 20 years). 30 of the 34 (88%) children had detectable anti-DT-GM antibody concentrations, ranging from undetectable to 191.4 mg/ml with a median of 1.5 mg/ml. Surprisingly, there was no difference between the anti-DT-GM antibody concentrations in the children with AML and 43 adult AML patients previously analyzed (Clin Immunol, in press; $p=0.7$). Out of the 34 children, only was one was positive by the bioassay, the child with the highest anti-DT-GM antibody concentration.
CONCLUSIONS: Although 88% of children with AML exhibited antibodies to DT-GM by EIA, only one child neutralized DT-GM by bioassay. These results indicate despite routine vaccinations against DTo that the majority of children with AML could undergo treatment with DT-GM.

358. Aventis Asthma/Allergy Research Award: The mechanism of anti-inflammatory activity of clarithromycin: inhibition of NF-κβ activation and TNF-α release. Rose Jung, Pharm.D., Douglas Fish, Pharm.D., Kathleen A. Stringer, Pharm.D., Robert Scheinman, Ph.D.; University of Colorado Health Science Center, Denver, CO.

PURPOSE: Clarithromycin has been shown to be effective in reducing prednisone requirements in patients with moderate corticosteroid-dependent asthma. This steroid-sparing activity has been attributed to the anti-inflammatory activity of macrolide antibiotics. The purpose of this study was to investigate the synergistic inhibitory effects of clarithromycin and prednisolone on lipopolysaccharide (LPS), phorbol myristate acetate (PMA), and interleukin-1 (IL-1)-induced NF-κβ and tumor necrosis factor-α (TNF-α) production in human bronchial epithelial cells and human peripheral macrophage.
METHODS: After stimulation with LPS, PMA, or IL-1, inhibition of NF-κβ by achievable serum concentrations of clarithromycin and/or prednisolone was determined using electrophoretic mobility gel-shift assay. A potential interaction between clarithromycin and glucocorticoid receptors was explored. Finally, a correlation between NF-κβ inhibition and TNF-α release was determined to validate the in vitro results.
RESULTS: The treatment of human bronchial epithelial cells and human peripheral macrophage cells with LPS, PMA, or IL-1 strongly activated NF-κβ. Preincubation with clarithromycin and/or prednisolone blocked the effects of the stimulators in a dose-dependent manner. Both clarithromycin and prednisolone resulted in significant inhibition of TNF-α production. The chloramphenicol acetyltransferase assay indicated that NF-κβ-dependent reporter gene expression was suppressed when pretreated with clarithromycin. Clarithromycin did not interact with glucocorticoid receptors.

CONCLUSION: This study indicates that both clarithromycin and prednisolone suppress the production of proinflammatory cytokines via inhibition of NF-κβ activation. The ability of these agents to inhibit translocation of NF-κβ is likely to be a significant event which may provide more complete anti-inflammatory response when used together.

359. Aventis Infectious Diseases Research Award: Identification of genes differentially expressed in fluconazole resistance in *Histoplasma capsulatum* by differential display RT-PCR. *P. David Rogers, Pharm.D., M.S.*, Katherine S. Barker, Ph.D., Rita M. Nahlik, B.S., Donna C. Sullivan, Ph.D.; University of Mississippi, Jackson, MS.

PURPOSE: The development of fluconazole resistance in *Histoplasma capsulatum* has been reported in AIDS patients failing fluconazole therapy. The purpose of this study was to identify genes differentially expressed in fluconazole resistant strains of *H. capsulatum* that might contribute to fluconazole resistance.
METHODS: Differential display (DD)-RT-PCR was used to compare mRNAs from an isogenic matched set of clinical isolates obtained from an AIDS patient who relapsed while being treated with fluconazole for disseminated histoplasmosis. Isolates were grown in equal number in brain heart infusion broth at 37°C in a shaking incubator to mid-exponential phase. Cell pellets were collected by centrifugation and RNA was isolated. 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 resolved on a 4% acrylamide/7M urea gel and auto-radiographed. Complementary DNA fragments corresponding to apparently differentially expressed mRNAs were recovered and sequenced.
RESULTS: Eleven cDNA fragments were identified representing mRNAs that appear to be differentially expressed in fluconazole resistance. Of these, 2 shared sequence identity to *Saccharomyces cerevisiae* genes. Of particular interest was the apparent up-regulation of a *PSE1* homologue.
CONCLUSION: *PSE1* has been shown to be necessary in the nuclear localization of the multidrug resistance transcription factor PDR1. Over-expression of *PSE1* may represent a novel mechanism of antifungal resistance in this organism.

360. Bristol-Meyers Squibb Primary Care Research Award: A dose-response for inhaled corticosteroids in children. *Patricia L. Marshik, Pharm.D.,* Hengameh H. Raissy, Pharm.D., Shawn M. Welch, Pharm.D., Mark Crowley, M.D., Alex Emery-Cohen B.S., H. William Kelly, Pharm.D.; University of New Mexico Health Sciences Center, Albuquerque, NM.

PURPOSE: To establish a non-invasive model for determining dose- response for the topical anti-inflammatory activity of inhaled fluticasone propionate (FP) measured by exhaled nitric oxide (eNO).
METHODS: A randomized, open-label, cross-over trial of children, 6-16 years old with stable asthma requiring daily FP. Following a run-in on the original dose, patients were randomized to one of the following treatments: twice the original FP dose or half the original FP dose. Between treatments, subjects returned to the original dose of FP for a washout. Each study period was 14 days. Clinic visits occurred at baseline and following each study period. Subjects completed daily dairy cards. eNO and spirometry were measured at each visit.
RESULTS: Thirteen subjects completed the study (mean age 11.3 years). The median dose of FP was 440 µg/day. Differences for eNO measurements, pre and post FEV1 and peak expiratory flow (PEF) between doses were not detected. Statistical analysis was completed using ANOVA. Data is mean ± standard deviation.

	Baseline	Original dose (run-in)	1/2 dose	Original dose (washout)	2X dose
eNO	16.6± 13.8	12.9± 4.4	13.5±5.2	13.9±7.7	13.6±6.0
Pre FEV_1 (%Predicted)	97.5 ± 21.5	97.0±14.2	96.5±14.6	93.1±16.9	95.1±17.9
Post FEV_1 (%Predicted)	106.8± 20.1	100.8±13.6	98.9±12.7	98.8±12.7	99.6±14.3
AM PEF (l/min)		341.2±89.1	339.7±95.6	333.7±102.6	350.0±100.2
PM PEF (l/min)		347.6±96.9	343.4±96.1	341.2±98.1	358.3±98.7

CONCLUSION: A dose response to FP was not found for eNO or measures of lung function in this group of asthmatic children stable on their original dose of FP.

361. GlaxoSmithKline Pharmacotherapy Research Award: Correlation between NF-κβ and changes in chlorzoxazone disposition following an acute phase response in humans. *Peter J. Van Ess, Pharm.D.,* Christina M. Charriez, Pharm.D., Rajna T. Tosheva, Ph.D., Steven I. Shedlofsky, M.D., Robert A. Blouin, Pharm.D.; University of Kentucky; VA Medical Center, Lexington, KY.

PURPOSE: Administration of *E. coli* lipopolysaccharide (LPS) causes variable changes in cytochrome P450 2E1 (CYP2E1) activity in humans, while in the rat, a consistent decrease is observed. This study was undertaken to determine if the observed variability in CYP2E1 activity following LPS administration in humans is related to inter-subject differences in the acute phase response (APR) as indicated by peripheral blood lymphocyte (PBL) nuclear factor kappa-beta (NF-κβ) activation.
METHODS: Six healthy male volunteers were enrolled in a balanced crossover study. A 250 mg oral dose of chlorzoxazone (CZN) was given 1 hour following the final LPS or saline dose. Serum and urine CZN, 6-hydroxychlorzoxazone (6OH-CZN), serum C-reactive protein (CRP), serum cytokines and white blood cells (WBC) were quantified. Activation of the individual NF-κβ p50/p65 diamer partners in PBLs were quantified by flow cytometry.
RESULTS: LPS induced an APR in all subjects as demonstrated by a significant ($p<0.05$) rise in temperature (2.45 ± 1.1ºF), pulse (23 ± 9.7 bpm), CRP (3.0 ± 0.5) and WBC count (4.1 ± 2.0 1000/ul). LPS treatment did not significantly alter CZN oral clearance (Clo) or 6OH-CZN formation clearance (Clf). Preliminary results, demonstrate a significant correlation between NF-κβ p50 activation and the changes observed in 6OH–CZN Clf. In addition, a significant increase in the 6OH-CZN glucuronide renal clearance was observed following LPS treatment (Saline; 6.4 ± 1.6 vs LPS; 10.2 ± 2.0 ml/min/kg; $p<0.05$).
CONCLUSION: Inter-individual variability in CYP2E1 activity as assessed by 6OH-CZN Clf following LPS administration may be due to differences in the LPS induced APR.

362. Pharmacia Applied Health Outcomes Research Award: Patient willingness to pay for lipid management services provided by pharmacists: an application of the contingent valuation method. *Karen Blumenschein, Pharm.D.*, Alan Zillich, Pharm.D., Patricia Freeman, Ph.D., Magnus Johannesson, Ph.D.; University of Kentucky, Lexington, KY; American Pharmacy Services Corporation, Frankfort, KY; Stockholm School of Economics, Stockholm, Sweden.

363. Wyeth-Ayerst Women's Healthcare Research Award: Fracture risks in long-term care: osteoporosis and hypovitaminosis D. *Mary E. Elliott, Pharm.D., Ph.D.,* Kim Petersen, M.D., Neil Binkley, M.D., Molly Carnes, M.D., David Zimmerman, Ph.D., Mara Kieser, R.Ph.; University of Wisconsin; Meriter Health Center, Madison, WI.

PURPOSE: Women in long term care facilities (LTCFs) face a 3-8% annual risk of hip fracture. Bone density testing is rarely available in LTCFs, however, and the perception that most residents have osteoporosis may hinder attempts to target those at highest risk for pharmacologic intervention. In the elderly, low vitamin D status triggers secondary hyperparathyroidism, bone loss, and fractures. The purpose of this study was to determine the prevalence of osteoporosis and vitamin D (D) inadequacy in one LTCF.
METHODS: Calcaneal bone density was measured by dual energy x-ray absorptiometry and 24-OH D by radioimmunoassay.
RESULTS: For the 49 participants, calcaneal bone densities varied over a wide range, with a median T-score of –2.5, range –4.7 to +1.7. For 56% of women 25-OH D was <20 ng/ml, values associated with secondary hyperparathyroidism. Only two women had levels >32 ng/ml, recently recommended as optimal D status. Only one-third of subjects received multivitamins or calcium supplements. Women with higher D intake exhibited higher levels of 25-OH D ($p<0.02$).
CONCLUSIONS: Osteoporosis was prevalent in this cohort of LTCF residents, but the broad distribution of T-scores suggests that targeting those at highest risk (lowest T-score) is feasible. Vitamin D inadequacy was common. Given the potential convenience, low cost, simplicity, and safety of a variety of vitamin D supplementation strategies, the present results suggest an ideal opportunity for consultant pharmacist intervention. Exploration of new vitamin D replacement strategies and their potential for decreasing fractures and health care costs is warranted.

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