Fourteenth Annual
LOUIS C. LITTLEFIELD
Celebrating
PHARMACY RESEARCH EXCELLENCE DAY

April 17, 2018

ABSTRACTS
FOURTEENTH ANNUAL LOUIS C. LITTLEFIELD
Celebrating
PHARMACY RESEARCH EXCELLENCE DAY
Carpenter-Winkel Centennial Suite, DKR-Texas Memorial Stadium, April 17, 2018

Introductory Comments by John H. Richburg, Ph.D., Chair of CPRED 10:00 am

Distinguished Faculty Lecture

Introduction by Dean Lynn Crismon, Pharm.D. 10:10 am – 10:15 am

Speaker: Kenneth S. Ramos, M.D., Ph.D., Pharm.B. 10:15 am – 11:15 am
Vice President for Precision Health Sciences
Professor of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
The University of Arizona College of Medicine, Tuscon, AZ
“Shifting Paradigms in Healthcare: Bench to Bedside Translation in Genomic Medicine”

Coffee Break 11:15 am – 11:30 am

Keynote Scientific Lecture

Introduction by Amanda Kitten, Graduate Student in Pharmaceutical Sciences 11:30 am – 11:35 am

Speaker: John G. Kuhn, RPh, Pharm.D., FCCP, FHOPA 11:35 am – 12:35 pm
Professor Emeritus, Division of Pharmacotherapy
College of Pharmacy, The University of Texas at Austin
“Repurposing FDA Approved Drugs for Cancer Therapy”

Lunch Break Pick up boxed lunches 12:35 pm

Lunch Time Presentations by Abstract Winners (10 min + 5 min Q&A)

Introduction by Dr. Richburg 12:50 pm – 2:15 pm

Undergraduate Program: Rodan Devega
“Alpha-Ketoglutarate-Dependent Dioxygenase (ALKB) Homolog 6 Protects Pancreatic Cancer Cells from Alkylating DNA Damage Cytotoxicity”
Mentor: Dawit Kidane

Professional Program: Kailee Gaines
“Hmgb3 As A Novel Molecular Target to Induce Cisplatin Sensitivity In Chemoresistant Ovarian Cancer Cells”
Mentor: Karen Vasquez
FOURTEENTH ANNUAL LOUIS C. LITTLEFIELD

Celebrating

PHARMACY RESEARCH EXCELLENCE DAY

Graduate Program: Hannah O'Mary
“An Approach to Targeting Anti-Inflammatory Agents to Chronic Inflammation Sites”
Mentor: Zhengrong Cui

Postdoctoral Program: Nicolas Blazanin
“Solar Ultraviolet (SUV) Irradiation-Dependent Activation of IFNγ/Stat1 Pathway in the Epidermis is Required for Keratinocyte Proliferation and Inflammation”
Mentor: John DiGiovanni

Resident Program: Daria Zaygorodnyaya
“A Comparison of Injectable Diazepam and Lorazepam in the Goal-Directed Management of Severe Alcohol Withdrawal”
Affiliation: Dell Seton Medical Center at The University of Texas

Scientific Poster Session

Poster Viewing time 2:15 pm – 3:45 pm
Odd posters manned from 2:15-3:00 pm, even posters manned from 3:00-3:45 pm
*Light refreshments will be served

Poster Award Winner Announcement 3:45 pm
***Poster Break Down – please do not remove posters until the conclusion of the event.
Kenneth S. Ramos, MD, PhD, is Associate Vice President for Precision Health Sciences, Associate Vice President for Research, Professor of Medicine in the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Medical Staff, Department of Medical Toxicology and Precision Medicine, Banner University Medical Center in Phoenix, and Director of the Center for Applied Genetics and Genomic Medicine as well as the MD-PhD Program at the University of Arizona – Tucson.

Dr. Ramos is an accomplished physician-scientist and transformational leader, designated as an associate of the National Academy of Sciences and elected member of the National Academy of Medicine. He has vast depth of experience across the tripartite mission areas of education, research, and clinical service, and is recognized throughout the world for his scientific contributions in the areas of genomics, precision medicine, environmental health sciences, and toxicology.

With formal training in pharmaceutical sciences, chemistry, biochemistry, pharmacology, and medicine, Dr. Ramos is helping to steer the changing landscape of medicine and healthcare. In this context, he leads several translational, clinical research, and educational programs that integrate diverse approaches to elucidate genomic mechanisms of disease and novel therapies for several oncologic, pulmonary, and vascular diseases. Dr. Ramos has also provided academic, executive, administrative, and scientific leadership in the areas of genetics and genomic medicine at several academic institutions, and over the course of his career, has positively influenced the career of numerous clinicians and scientists engaged in medical, veterinary and pharmaceutical practice. He is deeply committed to initiatives that advance modern technological applications to improve quality of healthcare and reduce both disease burden and health-associated costs. One of his primary areas of focus in partnership with Banner University Medical Center is the development of precision-health strategies and approaches to advance health-care delivery and outcomes.

With the highest ambition for excellence, Dr. Ramos works closely with the faculty and staff of University of Arizona Health Sciences to secure a place among the most outstanding institutions in the U.S. involved in the education of health professionals and the discovery of new cures for disease, thus helping to shape the future of healthcare.

A native of Ely, Nevada, Dr. Ramos spent his formative years in New York, Puerto Rico, and Texas. He is married to Irma Ramos, M.D., a pediatrician and public health practitioner, and has two children – Kristie, a medical student at the UA College of Medicine –Tucson, and Ken Alexander, an undergraduate student at the University of Arizona.
John Kuhn, RPh, Pharm.D., FCCP, FHOPA

Dr. Kuhn received his BS degree in Pharmacy (1972) from The University of Texas at Austin and earned his doctor of pharmacy degree (1977) through a joint program of The University of Texas College of Pharmacy and the University of Texas Health Science Center at San Antonio. Dr. Kuhn went on to complete a residency in Pediatric and Adult Oncology at the Health Science Center.

Dr. Kuhn is currently a Professor of Translational Oncology with The University of Texas, College of Pharmacy in Austin, TX and the University of Texas Health Science Center at San Antonio, TX. Dr. Kuhn’s current research and clinical focus is repurposing FDA approved drugs for cancer therapy.

Pharmacology of anticancer/biological agents has been the focus of Dr. Kuhn’s research over the last thirty plus years. Dr. Kuhn served as the Director of Pharmacology, Institute for Drug Development at the Cancer Therapy and Research Center in San Antonio, Texas from 1993 to 1997. He was the Director of Pharmacology Core for the North American Brain Tumor Consortium from 1995 to 2008 as well as the San Antonio Cancer Center from 1991 to 2004. Agents for which Dr. Kuhn has had an integral part in their development include ondansetron, fludarabine, paclitaxel, mitoxantrone, docetaxel, topotecan, irinotecan and pemetrexed. Dr. Kuhn is a co-holder of a US patent for an intramedullary catheter device (Osteoport). This device spurred the development of EZ-IO, which has changed emergency medicine practices for both adults and children. Dr. Kuhn has authored or co-authored over 400 peer-reviewed publications, abstracts and book chapters. Dr. Kuhn has been the acting editor, co-editor and special editor for the journal of Investigational New Drugs (IND): The Journal of New Anticancer Agents.

Dr. Kuhn is the recipient of a wide array of awards and honors, the Education Award from the American College of Clinical Pharmacy, the Guttman’s Distinguished Lecture Award from the University of Kentucky, College of Pharmacy and the Bertha Bouroncle Distinguished Lecture Award, Ohio State University. In 2006, the Hematology/Oncology Pharmacy Association named their annual Keynote Lecture in his name. Dr. Kuhn is the recipient of the 2007 ASHP Foundation Award for sustained contributions to the literature. He is a fellow of the American College of Clinical Pharmacy and Oncology/Hematology Pharmacy Association. Dr. Kuhn received the William J. Sheffield Outstanding Alumnus Award from The University of Texas College of Pharmacy in 2010.

Dr. Kuhn has been a member of several professional and scientific organizations including the, Central Texas Society of Hospital Pharmacist (President, 1982-1983), the Hematology/Oncology Pharmacy Association (President/Past President 2004-2006), and the American College of Clinical Pharmacy (Board of Regents, 2005-2008).

The most significant part of his career has been having a part in the education and training of outstanding Oncology/Hematology Pharmacy residents and fellows.
2018 Scientific Abstract Award Winners

Undergraduate Student

Rodan Devega  
Mentor: Dawit Kidane  
“Alpha-Ketoglutarate-Dependent Dioxygenase (ALKB) Homolog 6 Protects Pancreatic Cancer Cells from Alkylating DNA Damage Cytotoxicity”

Pharmacy Student

Kailee Gaines  
Mentor: Karen Vasquez  
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Graduate Student

Hannah O'Mary  
Mentor: Zhengrong Cui  
“Acid-Sensitive Sheddable Pegylated Nanoparticles for Targeted Delivery To Chronic Inflammation Sites”

Postdoctoral Fellow

Nicholas Blazanin  
Mentor: John DiGiovanni  
“Solar Ultraviolet (SUV) Irradiation-Dependent Activation of IFNγ/Stat1 Pathway in the Epidermis is Required for Keratinocyte Proliferation and Inflammation”

Pharmacy Resident

Daria Zavgorodnyaya  
Affiliation: Dell Seton Medical Center at University of Texas  
“A Comparison of Injectable Diazepam and Lorazepam in the Goal-Directed Management of Severe Alcohol Withdrawal”
ORGANIZATIONAL OVERSIGHT

John Richburg, Ph.D.
Gustavus & Louise Pfeiffer Professor in Toxicology
Associate Dean for Research and Graduate Studies
Chair of the Research Day Committee

JUDGES

Tyler Gums, Pharm.D., M.S.
Assistant Professor, Division of Health Outcomes and Pharmacy Practice
College of Pharmacy

Rana Ghosh, Ph.D.
Assistant Professor, Division of Molecular Pharmaceutics and Drug Delivery
College of Pharmacy

Kevin Dalby, Ph.D.
Johnson & Johnson Centennial Professor, Division of Chemical Biology and Medicinal Chemistry
College of Pharmacy

Laura Fonken, Ph.D
Assistant Professor, Division of Pharmacology and Toxicology

Kelly R. Reveles, Pharm.D., Ph.D
Assistant Professor, Division of Pharmacotherapy
College of Pharmacy
# Fourteenth Annual Louis C. Littlefield Pharmacy Research Excellence Day

April 17, 2018

## Abstract Listing

### Undergraduate

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### STAFF SCIENTIST

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Abstract 1

ALPHA-KETOGLUTARATE-DEPENDENT DIOXYGENASE (ALKB) HOMOLOG 6 PROTECTS PANCREATIC CANCER CELLS FROM ALKYLATING DNA DAMAGES CYTOTOXICITY

Rodan Devega Shengyuan Zhao, Janci Addison, Dawit Kidane
Division of Pharmacology and Toxicology, College of Pharmacy
Dell Pediatric Research Institute, University of Texas at Austin, Austin-USA

Body of Abstract: Introduction: Alpha-ketoglutarate-dependent dioxygenase (AlkB) is a DNA repair gene first found in E.coli and responsible to repair alkylating DNA damage. The AlkB homolog (ALKBH) enzymes are dioxygenases that directly reverse DNA alkylation damage caused by endogenous and exogenous environmental factors to maintain genomic integrity. To repair DNA methylation damage, the ALKBH enzymes transfer a methyl group from the DNA adduct onto 2-ketoglutarate and release succinate and formaldehyde as by-products. Nine AlkB homologues exist in humans (ALKBH1–ALKBH8 and FTO), but only ALKBH2 and ALKBH3 have been shown to have a similar enzymatic activity as that of the bacterial protein so far. However, our in-silico analysis from The Cancer Genome Atlas (TCGA) database shows that ALKBH6 is amplified and overexpressed in 20% of pancreatic cancer patients and associated with poor overall survival.

Hypothesis: To test the hypothesis that loss of ALKBH6 in pancreatic cancer leads to genomic instability and increase sensitivity to alkylating agents mediated chemotherapy.

Methods: We built AlkB deficient E.coli strains complemented with human ALKBH6 to determine the effect of ALKBH6 on the survival of bacteria under the treatment of different types of alkylating agents. In addition, we knocked down ALKBH6 with siRNA in pancreatic cancer cells and we assessed the survival and genomic stability under the treatment of alkylating agents.

Results: Here, we show that ALKBH6 rescues AlkB deficient E.coli when treated with alkylating agents and the effect is more significant in single stranded (ssDNA) versus double-strand DNA (dsDNA). Additionally, loss of ALKBH6 in pancreatic cancer cells induces sensitivity to alkylating agents and increase double strand breaks.

Conclusion: Our results demonstrate that ALKBH6 protects pancreatic cells from alkylating DNA damaging agents that may contribute for chemotherapeutic resistance.

Funding:

Class of Presentor: Undergraduate Student
COP Affiliation: Pharm/Tox

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Abstract 2

TRANS-GENERATIONAL PRENATAL ENDOCRINE DISRUPTING CHEMICAL EXPOSURE ON BEHAVIOR AND TIMING OF ADOLESCENCE

Erin Vasquez  
Lindsay Thompson & Andrea Gore  
College of Pharmacy, Division of Pharmacology and Toxicology, The University of Texas at Austin

Body of Abstract: Endocrine Disrupting chemicals (EDCs) are substances, typically man-made, that interfere with the functions of the hormone system. Two classes of EDCs are Polychlorinated biphenyls (PCBs) and Vinclozolin. (VIN). Previous studies showed that direct EDC exposure has behavioral and physical effects; however the effect of EDCs in future generations is less well-known. Ancestral EDC exposure may also cause certain physical and behavioral changes, especially when the original exposure occurs during critical stages of development. We bred 6 generations of rats, beginning with F0 dams that were exposed to EDCs late in gestation via intraperitoneal injection of either DMSO (as a control), Vinclozolin (VIN), or Aroclor (A1221), the latter at 1mg/kg. From the F1 offspring, one male (paternal) and one female (maternal) were used to breed to the F3 generation without additional EDC treatment. The F3 dams were then injected with either DMSO, VIN, or A1221 (same treatment or criss-cross design). Breeding continued without further treatment through the 6th generation. All six generations were monitored for timing of puberty (preputial separation in males and vaginal opening in females). In order to measure different behavioral patterns across different treatments, adult rats were placed in an elevated plus apparatus and allowed to roam freely for 5 minutes. Using Anymaze software, the test was recorded for further analysis tracking distance, time spent in the open/closed arm, freezing time, line crossing, and mean speed. Ancestral exposure to A1221 advanced puberty in F3 males of the paternal lineage, an effect not seen in females. A double hit of A1221 in the F0 and F3 generation delayed puberty in F4 females of the maternal lineage. For the elevated plus model, the number of line crossings were calculated as an index of activity. In the paternal lineage F4 generation the amount of line crossings in the male were greater in rats with an ancestral exposure to VIN. Thus, prenatal exposure to EDCs in F0 and F3 generations caused significant trans-generational effects in physiology and behavior, with results dependent upon maternal or paternal lineages, sex, and which EDC treatment was administered.

Funding:

Class of Presentor: Undergraduate Student  
COP Affiliation: Pharm/Tox

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SURFACE MODIFICATION OF GEMCITABINE-INCORPORATED ACID-SENSITIVE MICELLES INCREASES THEIR CYTOTOXICITY AGAINST MACROPHAGES AND TUMOR CELLS

Riyad Alzhrani, Zhengrong Cui, Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, the University of Texas at Austin.

Body of Abstract: Purpose: Previously our group reported an acid-sensitive micelle (AS) formulation using an acid-sensitive molecule synthesized by conjugating stearic acid with polyethylene glycol (PEG2000) with a hydrazone bond (i.e. PHC). The AS micelles incorporated with 4-(N)-stearoyl gemcitabine (GemC18) were significantly more effective than GemC18 incorporated in control acid-insensitive micelles. Mannose receptor and mannose-binding lectin have been reported on macrophages and several cancer cell lines, including liver and lung cancers. The purpose of this study is to test the feasibility of using mannose as a ligand on the surface of the GemC18-incorporated, acid-sensitive micelles to increase their cytotoxicity against some cancer cells and (tumor-associated) macrophages.

Method: The micelles were prepared by a modified thin-film hydration method. GemC18 in tetrahydrofuran was dried into a thin film under vacuum and rehydrated with an aqueous solution of PHC, with or without a mannose-stearate conjugate (M-C18) under vigorous stirring in an 80 °C water bath. The particle size and zeta potential of the micelles were determined using a Malvern Zetasizer Nano ZS, and GemC18 concentration was analyzed by HPLC. The micelles morphology was observed using transmission electron microscopy. The cytotoxicity of the micelles was evaluated in J774A.1 mouse macrophages and three murine cancer cell lines: Lewis lung carcinoma (LLC), M-Wnt mammary cancer, and Panc-02 pancreatic cancer cell lines.

Results: The sizes of the GemC18-incorporated ASM and AS micelles were 99 ± 10 nm and 106 ± 11 nm, respectively. The zeta potentials of the ASM and AS micelles were slightly negative -4 ± 1.1 mV and -5 ± 3.7 mV, respectively. The loading efficacy of GemC18 for AS and ASM is around 2 ± 1 %. TEM images show the micelles are spherical. The cytotoxicity data revealed that the GemC18-incorporated ASM micelles were significantly more cytotoxic than GemC18-incorporated AS micelles in all of the cell lines tested, but not more cytotoxic in Panc-02 cancer cells.

Conclusion: Surface-modification of our GemC18-incorporated acid-sensitive micelles can increase their cytotoxicity against tumor cells that express sugar binding proteins and macrophages, which is known to express mannose receptors.

Funding: National Institute of Health (NIH)

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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CONJUGATION OF TOBRAMYCIN TO POLY(ETHYLENE GLYCOL) IMPROVES MUCUS PENETRATION AND ACTIVITY AGAINST P. AERUGINOSA BIOFILMS IN A CYSTIC FIBROSIS-LIKE MUCUS BARRIER MODEL

Tania F. Bahamondez-Canas Hairui Zhang, Jasmim Leal, Hugh D.C. Smyth
The University of Texas at Austin, College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Purpose: Biofilms are highly resistant microbial communities that grown within a protective matrix and have been found in different infections such as cystic fibrosis (CF)-associated lung infections (1,2). Tob has reduced activity against P. aeruginosa biofilms due to ionic interactions with the biofilm matrix (3). Previously we demonstrated that PEGylated-tobramycin (Tob-PEG) had superior activity against P. aeruginosa biofilms compared to tobramycin (Tob) (4). The goal of this study was to optimize the method of conjugation and assess its activity in an in vitro CF-like mucus barrier biofilm model

Methods: We functionalized PEG according to Atassi and Manshouri (5). Then Tob was conjugated to PEG by three different methods: Our original method described by Du et al. (4) (Method A), and methods B and C adapted from Hermanson (6) and Ferguson et al. (7), respectively. The products were analyzed by 1H NMR. For in vitro evaluation of the drug performance, P. aeruginosa (ATCC® 15692TM) was grown as biofilms and treated with Tob and the Tob-PEG products for 24 h. Then, the Tob-PEG with the highest activity was evaluated alongside with Tob in a model comprising biofilms of a bioluminescent strain (PAO1::p16Slux) growing in the 24-well plates with a CF-like mucus barrier placed between the treatment solutions and the culture using Transwell® inserts. Luminometry, colony counting, and optical density at 600 nm were used to evaluate the survival of the bacterial cultures after 9h of treatment.

Results: A comparison of the Tob-PEG products from the different conjugation methods showed significant differences in reduction of biofilm proliferation after 24h of treatment. Method B (Tob-PEGB) produced the highest conjugation of PEG with Tob. In the CF-like mucus barrier model, Tob-PEG was significantly better than Tob in reducing P. aeruginosa proliferation after only 5 h of treatment (p<0.01). Finally, Tob-PEG caused a higher reduction in the number of surviving P. aeruginosa biofilm colonies compared to Tob (p<0.0001).

Conclusions: We demonstrated the significantly improved antimicrobial activity of Tob-PEG against P. aeruginosa biofilms compared to Tob using two conjugation methods. Tob-PEG had better in vitro activity compared to Tob against P. aeruginosa biofilms growing in a CF-like mucus barrier model.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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Phone Number
Abstract 5

THE DNA GLYCOSYLASE NEIL3 ACROSS ALL CANCERS

Christopher S. Chu, Alex W. Klattenhoff, Megha Thakur, Oahn Tran, and Dawit Kidane.
UT Austin, College of Pharmacy, Division of Pharmacology and Toxicology.

Body of Abstract: Introduction: Base excision repair (BER) is one of the main DNA repair pathways within the cell. The first enzymes within BER are the DNA glycosylases, which excise the damaged DNA base. NEIL3 is one of the glycosylases that is involved with the removal of oxidized DNA base lesions. NEIL3 mutations and expression changes have been associated with various tumors. It is known that NEIL3 expression is correlated with worse prognosis with cancer patients. It is not known what cancers follow this trend or what other DNA repair genes are associated with NEIL3. In addition, we examine the role of NEIL3 during replication stress.

Method: To address understating across all cancers, The Cancer Genome Atlas provisional data sets were query and analyzed based upon NEIL3 expression levels for 21 different cancers. Kaplan-Meir survival curves were generated based upon the segregation of individuals into either low expressing NEIL3 (z-score < 0.5) or high expressing (z-score > 0.5) to assess the impact of survival for each cancer type and genomic instability. we performed DNA combing, immunofluorescent staining, and clonogenic survival assay using PARP1 inhibitor (Olaparib) and ATR inhibitor (ADZ6738).

Results: The data indicates that high expression of NEIL3 is associated with lower overall survival with 7 different cancers. Overexpression of NEIL3 associated with increase mutation frequency and chromosomal instability. Our in vitro data showed that NEIL3 is localized at double strand break (DSB) sites during replication stress. Furthermore, loss of NEIL3 significant increase of spontaneous replication-coupled DSBs and impairs the recruitment of DNA repair proteins at DSB sites. Additionally; it was shown that NEIL3-deficient cells are sensitive to ATR inhibition alone and in combination with PARP1 inhibition.

Conclusion: Based on our in silicon and in-vitro experiment, NEIL3 is likely responsible to keep DNA replication fork integrity and modulate therapeutics treatment outcomes.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox

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Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox
Abstract 6

CANCER AS A PREDICTOR OF POOR OUTCOMES IN CLOSTRIDIUM DIFFICILE INFECTION AMONG A NATIONAL COHORT OF UNITED STATES VETERANS

Andrew Delgado Amanda K. Kitten1,2, Shrina Patel1,2, Kelly R. Reveles1,2
1UT Austin College of Pharmacy, Pharmacotherapy Division; 2The University of Texas Health Science Center at San Antonio, Pharmacotherapy Education & Research Center

Body of Abstract: Rationale: Prior studies have demonstrated higher Clostridium difficile infection (CDI) incidence and poorer health outcomes among cancer patients admitted to United States (U.S.) community hospitals. Robust observational data are needed to confirm this association and explore effective therapeutic options for cancer patients with CDI. The purpose of this study was to evaluate clinical outcomes and antibiotic therapies in U.S. Veterans Health Administration (VHA) CDI patients with cancer.

Methods: This was a retrospective cohort study of all adult outpatient or inpatient VHA patients with CDI from October 1, 2002 to September 30, 2014. CDI was identified using ICD-9-CM code 008.45 plus a positive stool test. Cancer patients were identified using ICD-9-CM codes and were stratified between solid and hematologic malignancies. Outcomes included 30-day mortality and hospital LOS >14 days. Logistic regression was used to compare CDI outcomes for patients with and without cancer and CDI cancer patients receiving metronidazole or vancomycin monotherapy. Propensity score matching was also conducted to compare CDI outcomes for cancer patients receiving metronidazole or vancomycin.

Results: 30,326 patients with a first CDI episode were included, of which 8,777 (28.9%) had cancer. CDI patients with cancer had higher 30-day mortality than non-cancer patients (29.0% vs. 17.7%; OR 1.44; 95% CI 1.33-1.55), but no difference in LOS >14 days (51.3% vs. 48.5%; OR 0.99; 95% CI 0.92-1.12). CDI patients with hematologic malignancies had higher 30-day mortality than solid tumor patients (35.1% vs. 28.3%; OR 1.85; 95% CI 1.56-2.19). Among CDI patients with cancer, 3,968 were treated with metronidazole and 953 with vancomycin. Vancomycin-treated patients had similar 30-day mortality (29.3% vs. 27.2%; OR 1.12; 95% CI 0.91-1.36), but higher LOS >14 days (45.4% vs. 42.6%; OR 1.70; 95% CI 1.39-2.07) compared to metronidazole-treated patients. Findings were similar in the propensity score-matched analyses.

Conclusions: Among a cohort of U.S. veterans with CDI, patients with cancer had higher 30-day mortality, but similar LOS. Cancer patients with CDI treated with vancomycin or metronidazole monotherapy had similar 30-day mortality.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmacotherapy

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Fourteenth Annual Louis C. Littlefield Celebrating Pharmacy Research Excellence Day
In Professional, Graduate, and Postgraduate Programs

Abstract 7

DELETION OF TWIST1 INHIBITS UV-B INDUCED HYPERPROLIFERATION IN MOUSE EPIDERMIS

Fernando Eguiarte-Solomon Okkyung Rho and John DiGiovanni

Body of Abstract: Non-melanoma skin cancers (NMSC) have one of the highest incidences in the United States with over 5 million diagnoses every year. The major risk factor for the development of NMSC is solar ultraviolet radiation consisting of both UVA and UVB. In epidermal keratinocytes, the damage caused by UVB radiation results in deregulation of both proliferative and survival signaling pathways that contribute to tumorigenesis. The transcription factor TWIST1 has been reported to be essential for the formation and invasiveness of chemically induced tumors in skin. Our group established that deleting TWIST1 in mouse epidermis results in arrested cell cycle progression in response to TPA treatment, which in turn prevented tumor growth. However, the impact of keratinocyte specific TWIST1 deletion on carcinogenesis caused by UVB radiation has not been clarified. In preliminary experiments, we found that primary mouse keratinocytes with TWIST1 knockout (KO) displayed an increase in the Sub-G1 phase that corresponded with the increase in apoptosis as shown by augmented Annexin V staining. Furthermore, deletion of TWIST1 in skin keratinocytes in vivo (using K5-Cre x TWISTfl/fl mice) led to increased sensitivity to UVB-induced apoptosis following a single exposure to 300mJ/cm2. Specifically, the anti-apoptotic regulators ATF4, sestrin2, and the Bcl family members were downregulated in the TWIST1 KO mice compared to wild-type mice. Additionally, UVB-induced epidermal hyperproliferation was also reduced in the TWIST1 KO mice. Proliferation analysis by Ki67 immunofluorescence staining as well as BrdU incorporation showed a significant decrease in TWIST1 KO epidermis. Correspondingly, protein levels for cell cycle regulators like c-myc, c-jun, p-Rb, and p21 were reduced in the absence of TWIST1. We are currently treating cohorts of TWIST1 KO and wild-type mice with chronic doses of UVB to assess skin tumor development and progression. In further experiments, we will use KO and transgenic mouse models to examine the role of TWIST1 in regulating proliferation and survival of keratinocyte stem cells during UVB induced skin carcinogenesis. These studies are expected to reveal new key regulators that can be targeted in novel therapeutic strategies aimed to interfere with the oncogenic functions of TWIST1 in the development of NMSC.

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Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox

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ROLE OF HIGH MOBILITY GROUP BOX PROTEINS IN NUCLEOTIDE EXCISION REPAIR-MEDIATED PROCESSING OF DNA INTERSTRAND CROSSLINKS

Jillian Gerberich Anirban Mukherjee, Karen Vasquez

Body of Abstract: Many traditional anti-cancer chemotherapeutic agents induce DNA interstrand crosslinks (ICLs), lesions that form covalent bonds between the DNA strands. ICLs are highly cytotoxic if not properly repaired because they can block basic cellular processes such as transcription and replication. Nucleotide excision repair (NER) is a critical repair mechanism in processing ICLs in human cells. In addition to NER, ICLs are also processed through DNA double-strand break repair pathways (e.g., homologous recombination) in S-phase. We have previously demonstrated that the high mobility group box protein (HMGB1), a non-histone architectural protein, can bind to site-directed ICLs with high affinity and modulate error-free repair processing of such lesions. In addition, we have found that HMGB1 associates with the NER damage recognition protein XPA in human cells and facilitates the recruitment of XPA to the damaged site. Further, we have demonstrated that HMGB1 can architecturally modify the damaged substrate by inducing negative supercoils, which is known to facilitate damage processing by NER. Two other members of the HMGB protein family, HMGB2 and HMGB3, are highly similar to HMGB1 in sequence and domain structure. Thus, we hypothesize that HMGB2 and HMGB3 also modulate NER processing of ICLs. To test this hypothesis we are using a mutation-reporter system to measure mutation frequencies and spectra generated by site-directed ICLs in human cells. Preliminary evidence suggests involvement of HMGB2 and HMGB3 in error-free processing of ICLs, although potentially via an alternative mechanism to that of HMGB1. Additionally, chromatin immunoprecipitation results indicate that HMGB3 may associate with XPA on site-directed ICLs. Future genetic, molecular biological, and biochemical assays will provide additional insight as to the roles of the HMGB proteins in ICL repair. The processing and repair of ICLs in human cells is not completely understood, and therefore a detailed study to define the molecular mechanisms of ICL processing is warranted. Identifying new proteins involved in ICL processing may lead to new pharmacological targets, which may help us to improve the outcome of cancer treatment.

Funding: n/a
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In Professional, Graduate, and Postgraduate Programs

Abstract 9

EXAMINING THE ROLE OF HIGH AFFINITY COPPER TRANSPORTER 1 GENE IN
FUNCTIONAL SPERMATOGENESIS AND CISPLATIN-INDUCED TESTICULAR TOXICITY

Rashin Ghaffari Kristin R. Di Bona, and John H. Richburg
Center for Molecular and Cellular Toxicology, College of Pharmacy, The University of Texas at Austin, Austin, Texas

Body of Abstract: Cisplatin (cDDP) is a highly effective chemotherapeutic drug. However, treatment with cDDP contributes to many adverse side effects including prolonged azoospermia in male patients. Although it is known that cDDP disrupts spermatogenesis, its main cellular target and mechanism responsible for its lasting effects on fertility remain unknown. The high affinity membrane copper transporter 1 (CTR1; SCL31A1) has been shown to be involved in cDDP uptake in both in vivo and in vitro studies. Our preliminary evaluation on mice testes indicates that CTR1 is predominantly expressed in primary spermatocytes and SCs. To examine the role of CTR1 in the testis as well as to discern the relative contribution between CTR1 in SC and GC to the lasting cDDP-induced disruption in spermatogenesis, we have developed two independent mouse models, with the conditional knockout of Ctr1 in either SCs (SC-KO; Amh-Cre, Ctr1fl/Δ) or GCs (GC-KO; Ddx4-Cre, Ctr1lox/Δ). Interestingly, GC-KOs exhibit a severe reduction in testis weight (~83% by PND 41) with almost complete depletion of GCs. On the other hand, SC-KO mice had indistinguishable testis weight and histology from their wild-type (WT; Ctr1fl/fl) littermates, with all stages of spermatogenesis present. However, the SC-KO testis and seminiferous tubules had significantly lower copper levels than their WT littermates. The SC-KO mice were further challenged with an acute dose of cDDP, where the SC-KO and WT mice were either exposed to a single high dose of 5 mg/kg of cDDP or equivalent volume of saline for 48 hours. We found that SC-KO mice had similar GC death compared to its SC-WT littermates. Platinum levels in testis tissue and in the seminiferous tubules of treated mice showed no difference between both genotypes, moreover no difference in intracellular platinum levels in cDDP-treated primary SCs derived from both genotypes. Taken together, these observations reveal for the first time 1) the required role of CTR1 in GCs, but not in SCs, for functional spermatogenesis and, 2) the compensatory mechanism for the SCs on cDDP acquisition independent to CTR1 pathway. Future investigations will utilize SC-KO as a mouse model to further study the testicular copper transport system, and the GC-KO mice will be utilized to explore the importance of CTR1 and/or copper on spermatogenesis.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox

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Abstract 10

STRUCTURAL INSIGHTS INTO THE PROMUTAGENICITY OF THE MAJOR OXIDATIVE ADENINE LESION 7,8-DIHYDRO-8-OXOADENINE

Myong-Chul Koag Michael Hawkins and Seongmin Lee*
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Body of Abstract: Reactive oxygen species attack DNA to produce 8-oxoguanine (oxoG) and 8-oxoadenine (oxoA) as major lesions. Structural basis for the mutagenic potential of oxoA, which has been shown to induce A to C transversions in vivo, remains poorly understood. To gain structural insights into oxoA-induced mutagenesis, we determined three crystal structures of oxoA-containing DNA in complex with human DNA polymerase β (polβ). When paired with dTTP, oxoA adopts an anti conformation and forms a Watson-Crick base pair in the active site of the enzyme. When paired with dGTP, oxoA adopts a syn conformation and forms a Hoogsteen base pair with a Watson-Crick-like geometry, underscoring the dual coding potential of oxoA. Kinetic studies show that polβ incorporates dGTP opposite oxoA with an efficiency comparable to dATP insertion opposite oxoG, suggesting that bypass of oxoA by DNA polymerases is promutagenic.

Funding:

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COP Affiliation: CBMC

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QUALITY-BY-DESIGN ANALYSIS OF SYNTHESIS CONDITIONS FOR GENERATING ANTI-BIOFILM IRON OXIDE NANOPARTICLES

Lara A. Heersema  Hugh D.C. Smyth

Body of Abstract: Purpose: Iron oxide nanoparticles have many potential medical and pharmaceutical applications; however, this nanotechnology has yet to impact the market in a meaningful way. The goal of this study is to use rigorous statistical analysis to determine the effect of high-temperature thermal decomposition synthesis conditions on iron oxide nanoparticle physicochemical properties to generate nanoparticles for anti-biofilm applications.

Methods: Based on preliminary experiments and literature review, six synthesis reaction parameters were selected for further evaluation using quality-by-design analysis. Specifically, we are evaluating reaction temperatures, time, atmosphere for each reaction in the two step process and drying conditions. Using a 14-run 2IV6-2 Definitive Screening Design we are able to evaluate parameter effects, second order interactions, and provide initial data for optimization. Physicochemical properties including size, crystal structure, and core shape are evaluated using dynamic light scattering, Raman microscopy, and transmission electron microscopy.

Conclusions: Iron oxide nanoparticle physicochemical properties are difficult to control due to limited research involving reaction conditions for high-temperature thermal decomposition synthesis and their effects on NP properties. Currently, published research has focused on only a handful of reaction parameters and on individual stages of the overall synthesis reaction. In contrast, this study holistically evaluated reaction parameters, which allowed us to determine both stages of the nanoparticle reaction can affect the physicochemical properties of iron oxide nanoparticles. Further analysis of these reaction parameters and optimization may allow for large-scale synthesis and incorporation of controlled nanoparticles in pharmaceutical products.

Funding: This material is based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. (DGE-1610403).

Class of Presentor: Graduate Student
COP Affiliation: Other
THE RELATIONSHIP BETWEEN CHRONIC DOXYCYCLINE USE AND HEART FAILURE: A RETROSPECTIVE COHORT STUDY

T. Matthew Hill, Pharm.D., Kenneth Lawson, Ph.D.

Body of Abstract: Over five million adults in the United States are currently living with congestive heart failure, with almost one million new diagnoses every year. The literature contains evidence in animal models that doxycycline exposure accelerates left ventricular hypertrophy, a precursor to heart failure. However, no evidence was found evaluating doxycycline’s long-term cardiac safety in humans. The primary objective of this study was to evaluate doxycycline use as a risk factor for heart failure. The secondary objective was to evaluate the presence of a dose-relationship.

Data from a large national health plan were used for the analysis. An initial random sample of 1,000,000 patients with hypertension (HTN) was selected from the data source. Pharmacy claims were used to identify patients with exposure to doxycycline. A control group was matched based on enrollment data, then patients were excluded pairwise if diagnoses associated with heart failure were observed during a pre-index period. Cox proportional hazards regression was used to estimate hazard ratios (HRs) for heart failure while controlling for covariates. To assess the secondary objective, a predictor for cumulative dose was added to the model. Graphical and analytical methods were used to assess the model assumptions for both objectives.

A total of 7,397 patients met inclusion criteria for exposure to doxycycline. Of those, 6,011 exposed patients were successfully matched to control patients. Of the 12,022 matched patients, 1,370 were excluded for pre-index events. After controlling for covariates, doxycycline exposure was not significantly related to diagnosis of heart failure in hypertensive patients (HR = 1.007, CI = 0.9681-1.0481). Although the dose-relationship between doxycycline and heart failure was significant, the HR was very close to 1 (HR = 1.00, CI = 1.00 – 1.00). There was no strong evidence of model assumption violations for either objective.

Clinically evaluating long-term doxycycline therapy is important as use continues. In summary, we did not observe an increased risk of heart failure in patients on doxycycline therapy. While these study results suggest that doxycycline therapy does not contribute to heart failure, clinicians should consider the potential benefits and risks of long-term doxycycline therapy.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: HOPP

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Abstract 13

NOVEL ULTRA-SMALL SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES WITH INCREASED DISTRIBUTION TO TUMOR TISSUES FOR POTENTIAL TUMOR THERANOSTICS

Stephanie Hufnagel Xu Li; UT Austin College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery
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Haiyue Xu; UT Austin College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery
Zhengong Cui; UT Austin College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Purpose: Ultra-small superparamagnetic iron oxide nanoparticles (USPIONs) have been studied as theranostic agents in imaging and treating cancer. These magnetic particles can be utilized as contrast agents for magnetic resonance imaging (MRI) of tumors as well as therapeutic agents via hyperthermia induced by a magnetic field. Feraheme® is an FDA-approved USPION product indicated for the treatment of anemia in chronic kidney disease. This product has been studied as a tumor theranostic agent, and more recently, was shown to inhibit tumor growth in mouse models. Unfortunately, Feraheme® was not intended to target tumor tissues. The present study was designed to increase the delivery of USPIONs to tumor tissues by a proprietary surface-modification.

Methods: Modified USPIONs were synthesized using a nano-precipitation method. The particle size was measured using a Malvern Zetasizer Nano ZS. The morphology of the particles was examined under a JEOL 2010F Transmission Electron Microscope (TEM), and the particle surface modification was visualized under TEM after negative staining. The effect of the proprietary surface modification of the USPIONs on their distribution to tumor tissues was preliminarily evaluated in a mouse model with orthotopic mammary tumor.

Results: The new USPIONs are spherical and 20-30 nm in diameter. When negatively stained, the entire particle size including the surface modification was shown to be closer to 50 nm (Figure 1, bar = 50 nm, inset shows negative staining). In mice with pre-established orthotopic M-Wnt mouse mammary tumor (6-9 mm), intravenous injection of our modified USPIONs increased the content of iron in tumor tissues by more than 50% when measured 24 h after injection, as compared to intravenous injection of Feraheme®.

Conclusion: Our new surface-modified USPIONs have the potential to significantly increase the delivery of ultra-small superparamagnetic iron oxide nanoparticles into tumor tissues after intravenous injection. Tumor theranostics using our new USPIONs is expected to be more effective than using Feraheme®.

Funding: This work was supported in part by a National Institutes of Health grant (CA135274 to Z.C.). Stephanie Hufnagel was supported by a fellowship from the American Foundation for Pharmaceutical Education. Solange Valdes is a winner of the Becas-Chile Scholarship from the Government of Chile.

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HIGH MOBILITY GROUP BOX PROTEINS FUNCTION IN PROCESSING DRUG-INDUCED DNA DAMAGE IN HUMAN OVARIAN CANCER

Van Huynh, Anirban Mukherjee, and Karen M. Vasquez,
Division of Pharmacology and Toxicology, Dell Pediatric Research Institute, College of Pharmacy, UT Austin

Body of Abstract: Ovarian cancer is the most lethal disease among gynecological cancers and accounts for the fifth most common cause of cancer death in women. The five-year survival rate is less than 50% and the risks from treatment including secondary malignancies, and disease recurrence remain high. A popular treatment for ovarian cancers is platinum-based chemotherapy to induce DNA damage such as DNA intrastrand crosslinks and DNA interstrand crosslinks (ICLs), which result in distortion of the DNA structure, inhibition of DNA metabolism and drive cell death. After DNA damage is recognized, the cells activate DNA damage responses, which include multi-protein networks to induce signal transduction processes and promote DNA damage repair to remove the lesions and maintain genomic stability. Defects in DNA damage responses and DNA damage repair are associated with a variety of human diseases including cancer. It has been recognized that the activation of DNA damage repair mechanisms is in part responsible for the sensitivity and resistance to DNA damaging agents including the platinum-based drugs in ovarian cancer treatment. As a result, a better understanding of the DNA damage repair mechanisms involved in ovarian cancer will guide improved strategies to treat ovarian cancer.

My project is focused on the functions of the High Mobility Group Box (HMGB) protein family, which exhibit high binding affinity to distorted DNA structures and we have found them to be involved in different DNA damage repair pathways. From a clinical perspective, HMGB proteins have been recognized to associate with disease etiology, treatment outcome, and drug resistance in ovarian cancer. Data from our lab have shown the involvement of HMGB proteins in recognizing and repairing chemotherapeutic DNA interstrand crosslinks. Furthermore, our results indicate differences between cisplatin-sensitive human ovarian cancer cells compared to cisplatin-resistant cells in DNA damage responses to ICLs follow Psoralen plus UVA (PUVA) treatment.

My hypothesis for this work is that the HMGB proteins are involved in processing chemotherapeutic drug-induced DNA damage in ovarian cancer, leading to drug resistance. The most toxic form of DNA damage resulting from platin-based drugs in ovarian cancer chemotherapy is the DNA interstrand crosslink (ICL), which can lead to DNA double-strand breaks (DSBs). We are using different methods to induce ICLs and DSBs in cisplatin-sensitive (A2780) and cisplatin-resistant (A2780-cis) human ovarian cancer cell lines to determine the mechanisms by which the HMGB proteins modulate the processing of these chemotherapeutic DNA lesions. The findings will enhance our understanding of the repair mechanisms involved in human cancer following treatment with DNA damaging chemotherapeutic agents, which in turn will facilitate development of better strategies to improve chemotherapeutic efficacy and prevent drug resistance.

Funding:

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haivanqt85@gmail.com
Body of Abstract: Introduction: KinetiSol® Dispersing (KSD) is a novel high energy mixing, fusion-based technique and is well established as a technology utilized to formulate amorphous solid dispersions (ASDs) [1, 2]. However, little effort has been made to analyze the KSD-processed materials with aims of analyzing homogeneity of the processed amorphous samples. Homogeneity, or blend uniformity, of amorphous samples is a critical parameter for stability and prevention of recrystallization upon storage. Our study seeks to analyze the homogeneity of KSD-processed materials using a previously studied, high melting point, poorly water soluble drug, meloxicam (MLX) [3].

Materials and Methods: MLX was hand-mixed with Kollidon® VA64 (VA64) and charged into the KSD chamber. Samples were prepared at 10, 5, and 1% w/w drug load for analysis of potency and homogeneity. Magnesium stearate (MgSt) 0.5% w/w was utilized to aid the flowability of the samples during processing and provide greater sample yield from the KSD chamber. Processed samples were milled and passed through a 125 µm sieve. Thermogravimetric analysis (TGA) was employed to analyze the degradation temperature of MLX. X-ray diffraction (XRD) was employed to determine amorphicity of the processed samples, and high-performance liquid chromatography (HPLC) was performed on all processed samples to determine potency of MLX. To effectively evaluate homogeneity, the least possible amount of processed material was solubilized in 10 mL diluent to a resulting MLX concentration of 100 µg/mL.

Results and Discussion: From TGA, we determined an onset of degradation at 150°C. Therefore, the optimal KSD processing parameters for the MLX-containing samples were determined to be an ejection temperature of 130°C and a rotation speed of 3250 rpm. All processed samples spent <30 seconds in the KSD chamber and were immediately quenched between aluminum plates once reaching the target temperature. All processed samples were confirmed amorphous via XRD. The sample potencies were 88.4%, 91.8%, and 100.6% for 10, 5, and 1% w/w samples, respectively. These values are consistent with expected potencies for KSD-processed materials, and only one sample had a variability of > 5% from the rest of its respective batch (n=3).

Conclusion: KSD is a technology that can be utilized to successfully generate ASDs and is capable of forming homogenous processed samples, as analyzed by HPLC.

Funding:

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Abstract 16

EVALUATION OF THE RISK OF STROKE IN RELATION TO THE USE OF 5-HT AGONIST AMONG SICKLE CELL DISEASE PATIENTS

Hyeun Ah Kang  Jamie C. Barner - UT Austin College of Pharmacy, Health Outcomes and Pharmacy Practice division
Brady S. Moffett2 - Texas Children’s Hospital, Houston, Texas, USA

Body of Abstract: Introduction: Prevalence of frequent headache among Sickle Cell Disease (SCD) patients is higher than the general population and half of SCD patients’ headache symptoms are consistent with migraines. Although there is no published evidence of the association between use of 5-HT agonists and the risk of stroke among those with SCD, 5-HT agonists are not recommended for these patients because of the perceived stroke risk. This study aimed to determine if there is an association between the risk of stroke and the use of 5-HT agonists among SCD patients in real world practice.

Methods: This was a retrospective nested case-control study using Texas Medicaid claims data from 9/1/11-8/31/15. Texas Medicaid enrollees who were <64 years, had ≥1 inpatient or 2 outpatient SCD diagnoses during the index period (9/1/12-8/31/15), and had no history of stroke before 9/1/12 were included. Cases included individuals with ≥1 stroke diagnosis (ICD9 = 433.xx, 434.xx) during the index period and controls consisted of a random sample of individuals without a stroke diagnosis. Cases and controls were matched on age, gender, and index date (1:5 matching) and their 5-HT agonist use within 1 year prior to the index date were compared. Descriptive statistics and multivariate conditional logistic regression analyses were conducted to determine whether the risk of stroke was associated with the use of 5-HT agonist while controlling for other covariates (transient ischemic attack, seizures, hypertension, use of hydroxyurea).

Results: Of included patients (N=4,801), 283 (6.1%) had a diagnosis of stroke during the index period. Three (1.1%) with stroke had ≥ 1 prescription for 5-HT agonist within 1 year prior to the stroke diagnosis as compared with six (0.4%) of the matched controls (odds ratio [OR] 2.50, 95% CI 0.63–10.00). After adjustment for covariates, logistic regression showed that use of 5-HT agonists was not significantly associated with the risk of stroke (OR 2.22, 95%CI 0.54–9.14).

Conclusion: This study revealed no association between the initiation of 5-HT agonist therapy among SCD patients and a risk of stroke. The results should be interpreted with caution and providers should evaluate the risks and benefits when prescribing 5-HT agonists to treat headaches in SCD.

Funding: n/a

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ASSOCIATION BETWEEN HORMONAL CONTRACEPTIVE USE AND DEPRESSION IN ADOLESCENTS

Ut Austin College of Pharmacy

Body of Abstract: Background: Contraceptive use among children and adolescents has increased from 48 percent in the early 1980’s to nearly 80% in 2010. Research has shown that adolescent females may be more susceptible to depression after initiating hormonal contraception. Most studies on contraceptive use are limited to adult populations and there remains a need to further explore the risk of depression in adolescents. The objectives of this study were to determine the incidence of depression and describe adherence patterns among adolescents during their first year after initiating oral contraceptive therapy.

Methods: A retrospective study design using Texas Medicaid claims data from January 1, 2012 to December 31, 2015 was used to identify incident users of oral contraceptive therapy. Continuously enrolled children and adolescents between 10 and 19 years of age newly initiating contraceptive therapy and having at least two prescription claims in the one-year follow up period were included. Patients were excluded if they had a mental health diagnosis 6-months prior to starting contraceptive therapy.

Results: 10,063 patients were continuously enrolled throughout the study period and used for all study analyses. A total of 1,184 individuals (12%) had a depression diagnosis in the one year follow up period. A majority of these adolescents were between 14 and 17 years of age. Further analysis will assess the medication adherence and persistence of adolescents that had a depression diagnosis in the 1-year follow-up period as well as unique trends in the contraceptive types that were predominantly used by these adolescents.

Conclusion: The results of this study show that 12% of children and adolescents had a depression diagnosis within 1-year of newly initiating contraceptive therapy. Adolescents may have an increased risk of developing depression after starting contraceptive therapy emphasizing the need to carefully evaluate and implement contraceptive use based on benefits and risks in this younger population.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: HOPP
Abstract 18

OUTPATIENT SULFONYLUREA PRESCRIBING TRENDS IN THE UNITED STATES BETWEEN 2009 AND 2015

Amanda Kitten, PharmD Kellie Reveles, PharmD, PhD, BCPS
UT Austin College of Pharmacy, Division of Pharmacotherapy, University of Texas Health San Antonio School of Medicine, Pharmacotherapy Education and Research Center

Body of Abstract: Purpose: A growing body of evidence over the last decade suggests that sulfonylurea use in the treatment of type 2 diabetes mellitus (T2DM) is harmful to patients due to beta-cell loss and the risk of hypoglycemia. The emergence of novel antidiabetic agents negates the need for sulfonylureas in T2DM treatment. The objective of this study was to measure the prescribing trends of sulfonylureas in the United States (US) given these developments in T2DM treatment.

Methods: This was a cross-sectional study using the Centers for Disease Control and Prevention’s National Ambulatory Care Survey (NAMCS). We included all patients with an outpatient visit between 2009 and 2015 and a diagnosis of T2DM. The primary outcome was overall and longitudinal rates of sulfonylurea prescriptions in the US. Sulfonylurea use was defined as a prescription for all glipizide, glyburide, and glimepiride formulations or any sulfonylurea combination product, as identified by Multum codes. Sulfonylurea prescription use was determined by dividing the number of patients who were prescribed any sulfonylurea by the total number of patients diagnosed with diabetes times 100%. Data weights were applied to determine national estimates. We also determined the rates of sulfonylurea prescriptions by payer and by Latino versus Not Hispanic or Latino populations.

Results: A total of 381 million patients were included in this study. The median age of patients was 64 years, and the male and female populations were equal, with each comprising 50% of the study population. The overall sulfonylurea prescribing rate for the study period was 24%. The rate of prescribing decreased from 24% in 2009 to 16% in 2015. The rate of prescribing in Hispanic or Latino patients was 19% overall, compared to 21% in the non-Hispanic or Latino populations. The rate of prescribing declined in all ethnicities over the seven-year period. From 2009 to 2015, the rate of sulfonylurea prescribing in Medicare patients decreased from 24% to 13%.

Conclusion: Overall sulfonylurea prescribing rates decreased from 2009 to 2015, with a decline seen across all ethnicities as well as in Medicare patients. Despite this decline, the 2015 rate was approximately 16%, indicating that provider education regarding the development of newer and safer T2DM treatment strategies is necessary.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmacotherapy

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Class of Presentor: Graduate Student
COP Affiliation: Pharmacotherapy
Abstract 19

GRANULATION MECHANISMS AND THE EFFECT OF PROCESSING CONDITIONS ON PHYSICOCHEMICAL PROPERTIES OF GABAPENTIN GRANULES PREPARED BY CONTINUOUS TWIN-SCREW EXTRUSION

Nada Kittikunakorn  David White, Tony Listro, Charlie Martin, Xin Feng, Feng Zhang

Body of Abstract: Twin-screw melt granulation (TSMG), a continuous process, offers many advantages over batch melt granulation process. Since it is a solvent-free process and offers higher mixing efficiency and compressibility improvement, TSMG is suitable for processing moisture-sensitive drugs and high-dose drugs. This study aims to investigate (1) the effect of binder type and binder particle size and (2) the effect of processing parameters on the physicochemical properties of gabapentin granules. Our goal is to establish a correlation between the formulation and process, the granule structures, and the granule properties.

Binary mixtures of thermal binder and GABA were processed using a Leistritz Nano 16 extruder. Three different types of binder (PEG 8000, Compritol ATO888, and HPC) and different particle size (Klucel ELF, Klucel EXF, and Spray-dried HPC) were evaluated as thermal binders. Processing parameters (feed rate, screw speed, and barrel temperature) were varied to study the effect of residence time and specific energy input on the physicochemical properties of gabapentin. Significant improvement in the compaction properties was achieved with TSMG for all three binders. HPC was more effective in improving the compressibility than PEG and Compritol 888 ATO. It was found that the size of GABA crystals was reduced inside the extruder by both conveying and kneading elements.

GABA-HPC granules contained higher level of GABA-L (0.10%) than GABA-PEG (0.01%) and GABA-Compritol (0.02%) granules. For GABA-HPC granules, GABA-L content increased with the decrease in HPC particle size. There was no significant difference in the compressibility of GABA granules containing HPC of different particle sizes. HPC EXF was selected to evaluate the effect of extrusion parameters on the properties of GABA granules. The degradation level decreased with the decrease in feed rate and increase in screw speed. Granules processed at high screw speed (300 rpm) and low feed rate (5 g/min) had the lowest degradant level at 0.03%.

This study demonstrated that TSMG is a viable method to prepare GABA granules to improve its compressibility, while maintaining its chemical stability. GABA granules with desired physicochemical properties can be achieved by optimizing the type of thermal binder, particle size of binder, and granulation parameters.

Funding: n/a

Class of Presentor: Graduate Student
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IMPACT OF OBESITY ON DNA STRUCTURE-INDUCED GENETIC INSTABILITY IN MICE

Pallavi Kompella Guliang Wang, John DiGiovanni and Karen M. Vasquez
Dell Pediatric Research Institute, Division of Pharmacology and Toxicology, College of Pharmacy, The University of Texas at Austin

Body of Abstract: Obesity is a growing global concern with studies reporting an elevated risk and poor prognosis for a variety of cancers in people with high body mass index. Obesity is thought to stimulate oxidative-stress that can cause DNA double-strand breaks (DSBs) and reduced DNA repair capacity. DSBs can result in gene translocations that can disrupt oncogenes in cancers such as Burkitt lymphoma (BL). The c-MYC oncogene in BL harbors vulnerable breakpoint “hotspots” enriched in repetitive DNA sequences that can adopt alternate DNA structures (i.e. non-B DNA; e.g. H-DNA). We found that H-DNA-forming sequences are intrinsically mutagenic in human cells and mice, and are substantially enriched at translocation breakpoints in human cancers. We speculate that the formation of non-B DNA structures can increase the accessibility of DNA to oxidative damage and impact DNA repair efficiency and accuracy. We hypothesize that obesity increases DNA structure-induced genetic instability in vivo, contributing to mutation “hotspots” in cancer. To detect obesity stimulated mutagenic potential of H-DNA, groups (n=4-5) of transgenic mice harboring a mutation-reporter with a human H-DNA-forming sequence (mapping to a breakpoint hotspot in BL) were put on control, 30% calorie-restricted (CR) diet and diet-inducing obesity (DIO) for 13 weeks. The mutation-reporter was recovered from mouse spleen, brain and liver tissues for blue-white mutagenesis assays. Results indicate that DIO significantly increased the mutagenicity of non B-DNA sequences in obese mice compared to mice on control and CR diets. The mutation spectra revealed deletions, point mutations and transversion events. Ligation mediated PCR on spleen genomic DNA detected a breakpoint hotspot at ~250 bp in DIO mice indicating the influence of obesity on the formation of H-DNA-induced DSBs. Next generation sequencing showed an increase in the number of point mutations and deletions in and around the H-DNA-forming sequence from obese mice. Our results to date suggest that obesity increases DNA structure-induced genetic instability. The results from the study will help in defining the molecular mechanisms underlying the effects of obesity on endogenous mutational “hotspots” and also aid in the development of strategies to prevent and/or attenuate the obesity-cancer link.

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IDENTIFICATION OF PEPTIDE SEQUENCES THAT FACILITATE DIFFUSION ACROSS MUCUS-LIKE BARRIERS

Jasmim Leal Tony Dong, Amber Taylor, Emily Siegrist, Hugh D. C. Smyth, Rana Ghosh

Body of Abstract: In cystic fibrosis (CF), mucus has increased viscoelasticity and higher concentration of covalent and non-covalent physical entanglements than in homeostasis, which greatly hinders permeability and transport of drugs and particles across the mucosae for therapeutic delivery. While recent studies have shown hydrophilic, net-neutral charge polymers can improve transport and minimize interactions with mucus, there is a dearth of alternative carriers that achieve rapid transport with desired cell uptake and drug release characteristics. Here, the objective of this work is to use phage display libraries to identify peptides that facilitate rapid transport across the mucus barrier. These combinatorial libraries possess a large diversity of peptide-based formulations ($10^8$ - $10^9$) to achieve unprecedented screening of potential stealth-like peptides that penetrate through mucin. An M13 phage peptide library was iteratively screened against a CF mucus-like model to identify peptides with the ability to penetrate through mucus. Selected phage clones displaying peptides and their fluorescent conjugates were assayed against CF-like mucus and saline to quantify their diffusivities. Phage clones and peptides conjugates presented up to 2.5-fold enhanced diffusivity in CF-mucus compared to controls (non-engineered phage or free fluorescein). While further studies are needed, these initial findings suggest that this biomolecule-based strategy may be translated to improve transmucosal delivery of drug delivery systems.

Funding: PhRMA Foundation, NIH R01HL138251

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics
Abstract 22

AN EVALUATION OF DATABASE STUDIES PUBLISHED IN THE JOURNAL OF MANAGED CARE & SPECIALTY PHARMACY: REPRODUCIBILITY USING ISPE-ISPOR REPORTING CRITERIA

Yi Liang (co-first author), Joshua Toliver (co-first author) Yi Liang1 (co-first author), Joshua Toliver1 (co-first author), Karen Rascati (corresponding author)
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Body of Abstract: Background: Studies using healthcare databases may suffer from insufficient transparency in reporting study details. This can reduce comparability, consistency, quality and confidence of evidence generated by database studies. A checklist of reporting criteria was developed by a joint ISPE-ISPOR task force in 2017 to improve transparency and reproducibility for healthcare database studies.

Objective: To evaluate the extent to which database studies published in the Journal of Managed Care & Specialty Pharmacy (JMCP) met the ISPE-ISPOR checklist criteria.

Methods: Database studies using claims data published in JMCP during the past year were assessed independently by two evaluators (YL and JT), using the ISPE-ISPOR checklist. The checklist has 9 domains (43 parameters). Each parameter was judged and reported as yes, no or not applicable. Results were summarized using descriptive analysis.

Results: Eighteen claims database studies were included in this analysis. All studies reported data providers, source data range, type of data and data linkage if applicable, but no information about the date of data extraction or data cleaning. No studies included a design diagram for overall study design. Regarding inclusion/exclusion criteria, all studies reported index date, sequencing of exclusions (flow diagram), enrollment windows and gaps. Washout for exposure and outcomes were also reported if applicable. All studies reported the definitions of event date for outcomes if applicable. All studies described the covariate assessment window and comorbidity scores, and all reported healthcare utilization metrics when using healthcare utilization as covariates. Eight studies (44%) did not report the detailed codes for covariate diagnosis or complications. When control sampling was used, all studies reported sampling strategies, matching factors and ratios. Finally, 6 studies (33%) did not mention the software used for statistical analysis.

Conclusion: Database studies published in JMCP from 2016 to 2017 reported most of the parameters, when applicable, recommended by the ISPE-ISPOR criteria. Future articles might need improved reporting of several parameters, such as data cleaning, design diagram, codes for covariates and type of statistical software used, if allowed by JMCP’s page and table limits.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: HOPP

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Abstract 22
PREVALENCE, RISK FACTORS, AND HEALTHCARE UTILIZATION FOR PNEUMONIA IN INDIVIDUALS WITH AND WITHOUT DIABETES MELLITUS IN THE UNITED STATES

KeTing Liu Grace C. Lee, PharmD, PhD; The University of Texas at Austin College of Pharmacy, Pharmacotherapy Division and The University of Texas Health San Antonio, San Antonio, TX

Body of Abstract: Background: Individuals with diabetes mellitus (DM) have been associated with increased risk for pneumonia. However, little is known about this population.

Objective: To describe the prevalence, risk factors and healthcare utilization patterns for pneumonia in individuals with DM, without DM and with DM-complications.

Methods: This was a retrospective, cross-sectional analysis of the U.S. adult population using Medical Expenditure Panel Surveys data from 2014. DM was defined by the Clinical Classification Software codes, 049 and 050; pneumonia was defined by the CCS code 122. DM-complications included diabetic retinopathy and nephropathy. Prevalence of pneumonia was compared using population-based rates (per 1000 persons) and risk ratios (RR). We analyzed healthcare utilization rates of individuals with DM, without DM and with DM-complications, based on care settings (outpatient clinic, emergency department (ED) and inpatient hospital). Data weights were applied to derive national estimates. A multivariable regression model was used to identify risk factors associated with pneumonia. A p-value <0.001 was used to determine statistical significance.

Results: The data represented 24 million individuals with DM and 218 million without DM in the U.S. A quarter of those with DM had DM-complications. The population-based rate for a pneumonia event was 34 per 1000 persons for individuals with DM and 19 per 1000 persons without DM. In the overall cohort, the most common pneumonia treatment setting was outpatient clinics (65% of all visits). Compared to the non-DM group, individuals with DM had 2.6x higher risk for hospitalization (RR: 2.61; 95% CI: 2.60 -2.62), 1.8x higher risk for ED visits (1.82; 1.81-1.84) and 1.4x in outpatient visits (1.44; 1.43-1.44). Similar trends were identified when comparing individuals with DM-complications to those without. Among individuals with DM, female sex, insulin-containing regimens, duration of DM, and length since last influenza vaccine were significant factors associated with a pneumonia event.

Conclusions: Individuals with DM, particularly those with DM-complications, have substantially higher healthcare utilization for pneumonia events. Clinical consideration of specific risk factors among individuals with DM may be warranted for preventative efforts.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmacotherapy

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THE COMPARISON OF DRUG RELEASE MECHANISM AND PHYSICAL STABILITY OF WEAKLY BASIC DRUG AND HYDROCHLORIDE SALT FROM SUSTAINED RELEASE HYDROPHILIC MATRICES PREPARED BY HOT MELT EXTRUSION

HYDROCHLORIDE SALT FROM SUSTAINED RELEASE HYDROPHILIC MATRICES PREPARED BY HOT MELT EXTRUSION

Xu Liu Eucharist Kun Feng Zhang

**Body of Abstract:** This study examines polyelectrolyte complex formation through acid–base reaction during the melt extrusion of Eudragit L100-55 and two different forms of lidocaine (free base or hydrochloride salt). It investigates the effects on the physical stability and dissolution properties of the extrudate granules with 30% drug loading. The physicochemical properties of extrudates are characterized using DSC, PLM, XRPD, ATR-IR, and Raman spectroscopy. The PLM and XRPD results indicate that both the lidocaine freebase (LC) and the lidocaine hydrochloride salt (LH) were amorphous or in molecular state in the polymer carrier. The ATR-IR and Raman spectroscopy results imply that the acid–base reaction between the drug and polymer occurred only in the LC extrudate. Due to the ionic drug–polymer interaction, the LC extrudate was physically more stable than the LH extrudate. Dissolution testing was performed in water and in buffers at different pH levels. The microenvironment pH was measured and the dissolution data were fit to a mathematical model to determine the mechanisms that control drug release. The extrudates of the two forms of lidocaine demonstrated distinctive release properties due to differences in solubility, drug–polymer interactions, and microenvironment pH. It is concluded the form of drug selection in melt extrusion resulted in different drug–polymer interactions and distinctive physical and chemical properties.

**Funding:** n/a

**Class of Presentor:** Graduate Student

**COP Affiliation:** Pharmaceutics

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LIMITATION OF THE FDA-RECOMMENDED DISSOLUTION METHOD FOR ITRACONAZOLE SOLID DISPERSIONS

Tongzhou Liu Feng Zhang, UT Austin College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Purpose: The objectives of this study are: (1) to study the dissolution and supersaturation behaviors of itraconazole amorphous solid dispersion (ASD) in the dissolution medium in the FDA-recommended dissolution method of ITZ tablet, and (2) to develop a discriminatory dissolution method for ITZ ASDs. We have found that the FDA-recommended dissolution method was not able to differentiate the samples of different degree of mixing between HPMC and amorphous ITZ.

Methods: UV spectroscopy, fluorescence decay, and ultrafiltration were employed to characterize ITZ self-association and its association with HPMC in 0.1 N HCl solution. Three amorphous ITZ samples (35% ITZ and 65% HPMC) with different degrees of mixing were prepared. Low-energy-input and high-energy-input ITZ ASDs were extruded using HAAKE™ MiniLab and Leistritz ZSE 18 HP-PH extruder, respectively. Amorphous ITZ was prepared by spray drying. Both 0.01 N HCl solution and pH 3.0 citrate buffer were evaluated as the alternative dissolution media. Samples were withdrawn at predetermined time points and filtrated with 1.0 µm Nylon filter for analysis.

Results: 0.1 N HCl solution could not discriminate ITZ-HPMC ASDs of different levels of mixing (homogeneous at the molecular level, vs. phase-separated, vs. physical mixture). With a similarity factor (f2) of 51, the dissolution profiles of “melt-extruded ITZ ASD” and the “physical blend of HPMC and amorphous ITZ” in 0.1 N HCl solution were statistically same. Our study has confirmed that ITZ neither self-associate nor associate with HPMC in 0.1 N HCl solution. Sustained supersaturation (greater than 2 months) of ITZ in 0.1 N HCl solution was due to the intrinsic low crystallization tendency of ITZ. Our data suggested that 0.01 N HCl is a more suitable method to characterize ITZ ASD. In 0.01 N HCl solution, the amount of ITZ in nanoparticles in the dissolution samples for high-energy-input ITZ ASD was significantly greater than (P<0.001) that for low-energy-input ITZ ASD.

Conclusion: The FDA-recommended dissolution method of ITZ tablet is not able to differentiate ITZ ASDs with different degree of mixing. 0.01 N HCl is a more suitable dissolution-testing medium for amorphous ITZ ASDs. The amounts of nanoparticles released from ITZ AZDs in 0.01 N HCl solution were significantly different, depending on the degree of mixing.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics
INTRACELLULAR UPTAKE OF SERUM ALBUMIN NANOPARTICLES IN ONCOGENIC KRAS CANCER CELLS BY MACROPINOCYTOSIS

Xinquan Liu  Rana Ghosh
University of Texas at Austin, College of Pharmacy, Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Nano-drug delivery systems have been designed and developed to deliver drugs to achieve higher therapeutic efficacy. Targeting ligands have been used to functionalize the nanoparticles to make further improvement of the delivery efficiency and minimizing side effects. However, challenges for effective targeted delivery should be overcome, including selection of ligand/target, conjugation chemistry and heterogeneity of the tumor microenvironment. The metabolism of cancer cells with KRAS mutation was altered. Those cells actively engulf albumin as a source of nutrients for survival. Taking advantage of this, we developed cross-linked albumin nanoparticles to improve the intracellular uptake in KRAS-mutated cancer cells without the need of targeting ligands. Albumin nanoparticles were synthesized by desolvation method and cross-linked by glutaraldehyde. The nanoparticles were labeled with fluorescein isothiocyanate (FITC-NPs) and characterized. Intracellular uptake of the FITC NPs were evaluated in KRAS mutated cell lines and wild-type KRAS cell lines. The size of the FITC-NPs was 73.62 ± 0.24 nm in diameter with the polydispersity index of 0.193 ± 0.002 and zeta potential of -42.40 ± 0.17 mV. Increased cellular uptake of FITC-NPs was observed comparing to monomeric albumin. The amount of FITC-NPs taken up in KRAS mutated cells were higher comparing to wild-type cancer cells. Preliminary results showed that macropinocytotic inhibitor (EIPA) could inhibit the uptake of the FITC-NPs greatly in mutated cells, indicating the endocytic pathway through macropinocytosis. These results indicated that cross-linked albumin nanoparticles could serve as a potential delivery system with increased uptake in KRAS-mutated cancer cells. For future studies, the direct relationship between KRAS mutation and the improved uptake can be evaluated by looking into the uptake in KRAS-mutated cells and KRAS mutation knocked-out cells, and further confirm the effect in animal models.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics
Abstract 27

THE IMPACT OF POLYETHYLENE OXIDE SEGMENT CONTENT ON THE DIFFUSION OF A HYDROPHILIC DRUG THROUGH POLYURETHANE MEMBRANES

Michael B. Lowinger, Feng Zhang, Robert O. Williams III
Molecular Pharmaceutics & Drug Delivery, College of Pharmacy, University of Texas at Austin

Body of Abstract: Since their introduction over 50 years ago, polyurethanes have been applied to nearly every industry. Polyurethanes are a group of condensation polymers that are typically synthesized by a step-growth polymerization reaction between isocyanates and polyols in the presence of a suitable catalyst. Their chemical diversity allows for a wide variety of properties, which can be effectively used to tailor drug release. Long-acting parenteral dosage forms, such as subdermal implants and intravaginal rings, are well suited to the use of a polymer with broad tunability of properties, enabling release kinetics to be tailored to the physicochemical and potency characteristics of a particular drug. Other polymers used to moderate drug release from long-acting parenteral formulations are generally hydrophobic, hindering a formulator’s ability to tune release rate for hydrophilic drugs. A polyether-based polyol particularly relevant to this research is polyethylene oxide (PEO). PEO-based polyurethanes exhibit water sensitivity due to the hydrophilicity and water-absorbing capacity of the ethylene oxide units. This study explored the impact of PEO segment content in the polymer on the diffusion of the hydrophilic drug emtricitabine through polyurethane membranes. The extent of polymer swelling when immersed in water was used as an indicator of PEO content. The investigation found that drug flux through the polyurethane membrane increased by approximately 1000-fold when comparing a polymer with negligible water swelling to one that swells to approximately 500% weight gain. The study may be used to simulate release from a drug-filled core through a rate-controlling membrane in a sustained-release dosage form. Future work will investigate the ability to design the release rate of the hydrophilic drug by mixing polymers of different PEO content in the rate-controlling membrane.

Funding: Merck Laboratories

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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ROLES OF HMGB PROTEINS IN MODULATING THE PROCESSING OF ALTERNATIVELY STRUCTURED DNA IN MAMMALIAN CELLS.

Pooja Mandke Anirban Mukherjee, Karen M. Vasquez.
UT Austin College of Pharmacy, Division of Pharmacology and Toxicology

Body of Abstract: The high mobility group box (HMGB) proteins are the most abundant non-histone DNA binding proteins in mammalian cells. It is comprised of 4 proteins (HMGB1-4) that share structural similarity; however, our preliminary mechanistic work in cells, and published reports from other groups on HMGB knockout mice phenotypes, suggest that the HMGB proteins possess distinct functions. These proteins have been implicated in the development and progression of several types of cancers, where its overexpression is correlated with poor prognosis and tumor aggressiveness. HMGB proteins can bind to alternative or (non-B) DNA structures with high affinity. Non-B DNA structures can form at repetitive DNA sequences, are enriched at “hotspots” of genetic instability in cancer and co-localize with deletion and translocation breakpoints in human cancer implicating non-B DNA in cancer etiology. Our lab was the first to report that naturally-occurring sequences capable of forming non-B DNA structures (e.g. H-DNA and Z-DNA) stimulate genetic instability in the form of DNA double-strand breaks (DSBs) in mammalian cells and mice, and are enriched at translocation breakpoints in human cancer. Further, we have data to suggest a role for the nucleotide excision repair (NER) nuclease complex ERCC1-XPF in processing mutagenic non-B DNA structures. ERCC1-XPF is important in NER and DSB repair, and its role in different repair pathways depends on specific protein-protein interactions. We have found that ERCC1-XPF cleaved H-DNA-forming sequences (NER-dependent cleavage) and Z-DNA-forming sequences (NER independent cleavage) in vitro leading to an increase in deletions and subsequent mutagenesis. We have also found that HMGB1 and NER proteins interact cooperatively to promote error-free repair of DNA damage. In contrast, our preliminary data suggests that HMGB3 is involved in the mutagenic repair of such structures via DSB repair. Since HMGB proteins may be associated with distinct repair mechanisms and the H-DNA- and Z-DNA-forming sequences appear to be processed by different repair mechanisms, here we will explore the impact of HMGB proteins on naturally-occurring genomic H-DNA/Z-DNA sequences. We hypothesize that HMGB1 and HMGB3 proteins modulate the processing of alternatively structured DNA via distinct DNA repair mechanisms.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Other
FACTORS ASSOCIATED WITH OPIOID PRESCRIBING AFTER OUTPATIENT SURGICAL PROCEDURES IN MEDICAID-ELIGIBLE YOUTH

Landon Z Marshall  Timothy M Hill, Sabina O Nduaguba, Hyeun Ah Kang, James P Wilson

Body of Abstract: Introduction: In light of the CDC’s guidelines on opioid prescribing, the benefits of prescription opioids in the pediatric population has been recognized. Further, the American Academy of Pediatrics and American Pain Society recognize the need for “humane and competent treatment of pain and suffering in all infants, children, and adolescents”. Despite the body of evidence supporting the effectiveness of opioids for controlling pain and the subsequent harms of uncontrolled pain, opioids remain a critical issue due to the resulting consequences associated with their misuse and abuse. This study aimed to identify factors associated with prescribing opioid therapy after outpatient surgical procedures.

Methods: This retrospective study used medical and prescription claims data from the Texas Medicaid database. Individuals who had at least one outpatient surgery between 07/01/12 - 12/24/15, aged between 5 and 17 at the date of the surgery, and continuously enrolled in for at least 6 months before the procedure date were included. Those who received any opioid prescription claim within 6 months before outpatient procedure were excluded. Opioid prescriptions within 7 days before and after the procedure were analyzed and a multivariate logistic regression was conducted to identify the factors associated with opioid prescriptions.

Results: A total of 51,145 patients (8.2 ±3.4 years) met the inclusion criteria. A majority of patients had an ear-nose-throat (ENT) (52%) or dental (36%) procedure. Twenty-five percent (10% for schedule II and 15% for schedule III-V) were prescribed an opioid within seven days of the procedure. Female gender, age, and procedure year were associated with higher odds of being prescribed an opioid. The odds of being prescribed an opioid were higher among patients who had an ENT, a gastrointestinal, or a urological procedure, and lower among patients who had a cardiovascular or dental procedure.

Discussion: This study showed that one-quarter of patients undergoing select outpatient surgeries were prescribed opioid pain medications. While certain patient characteristics were associated with greater odds of being prescribed an opioid pain medication, the actual use patterns of these drugs remains unknown. This analysis provides preliminary evidence regarding the use of opioids for pain management following outpatient surgeries.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: HOPP

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Abstract 30

MOLECULAR MECHANISMS FOR THE ASSOCIATION BETWEEN A SALICYLANILIDE DERIVATIVE (RAFOXANIDE) AND POVIDONE FOR AMORPHOUS SOLID DISPERSION PREPARATION

Fan Meng Zhifeng Jing, Yongchao Su, Rui Ferreira, Pengyu Ren, Marco Gil and Feng Zhang

Body of Abstract: Introduction: The effect of solvent composition on the interaction between RAF and PVP was investigated in the current study. Rafoxanide (RAF), a poorly water-soluble surface-active drug, is a derivative of salicylanilide. We investigated two solvent systems: (1) aqueous cosolvent, and (2) organic cosolvent. It was observed in our previous study that RAF-PVP feed solutions for spray drying behaved differently depending on the cosolvent composition.

Method: 1H NMR was used to identify the functional groups involved in the RAF-PVP association. 2D NMR Nuclear Overhauser effect spectroscopy (NOESY) and diffusion order spectroscopy (DOSY) were employed to evaluate the strength of associations between RAF and PVP, as well as the change in molecular mobility. Isothermal titration calorimetry (ITC) was used to determine the thermodynamic parameters of the association. Molecular modeling was used to illustrate the optimized geometries and association pattern between RAF and PVP.

Results: For RAF-PVP system in aqueous cosolvent, 1H NMR peaks of protons near the RAF amide group shifted to the lower field, indicating the formation of strong hydrogen bond between the amide group of RAF and the carbonyl group of PVP. In contrast, no chemical shift was observed for RAF when organic cosolvent was used. NOESY spectra of RAF-PVP system in aqueous cosolvent showed that protons in different benzene rings of RAF are coupling with each other, indicating the presence of RAF-RAF stacking. Similar diffusion coefficients for RAF and PVP from DOSY testing indicated a strong association between RAF and PVP. Molecular modeling demonstrated the association pattern consists a combination of hydrogen bonding between PVP and RAF, and

Conclusion: Both hydrophilic and hydrophobic interactions are two mechanisms contributing to the RAF-PVP association in aqueous cosolvent. The amide group of RAF forms strong hydrogen bond with the carbonyl group of PVP. Meanwhile, the stacking between benzene rings in different RAF molecules helps stabilizing the hydrogen bonding. RAF acted as a “linker” molecule, favoring the physical crosslinking of PVP chains. In organic cosolvent, no obvious interaction was observed between RAF and PVP.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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Abstract 30
Fourteenth Annual Louis C. Littlefield Celebrating Pharmacy Research Excellence Day
In Professional, Graduate, and Postgraduate Programs

Abstract 31

HIGH DIFFUSIVITY PEPTIDE SEQUENCES AS DRUG CARRIERS IN TUMOR EXTRACELLULAR MATRIX

Rashmi P. Mohanty

Rashmi P. Mohanty and Dr. Rana Ghosh
UT Austin College of Pharmacy, Molecular Pharmaceutics and Drug Delivery.

**Body of Abstract:** Cancer therapeutics for targeted cells is are limited by the diffusive transport through the tumor Extracellular extracellular Matrix matrix (ECM). Diffusivity of therapeutic macromolecules depends on their size, charge, configuration, and their interactions with ECM. We aim to design fast diffusing, nano-sized peptide sequences as drug carriers for improved drug delivery through a tumor microenvironment. We hypothesize that using phage display and Next Generation DNA sequencing (NGS) method can identify and optimize desired physicochemical properties that improve diffusivity of macromolecules through the tumor ECM. Therefore, we are shortlisting potential peptide sequences with the faster diffusivity through the an in vitro model of tumor ECM from a random phage-presenting peptide library. The peptide sequences are displayed on the surface of T7 phage with each phage expressing a different peptide sequence and effectively serves as a formulation with unique surface chemistry. Then, we screen the potential sequences with fast diffusivity by making the library to diffuse through the tumor ECM. Repeated rounds of selection are performed to narrow down the diversity and screen potential sequences with the specific desired characteristics. The peptide clones are analyzed by NGS method, as the phage genome genetically encodes the displayed peptides. Further, the screened clones are validated by comparing the diffusivity of the specific peptide sequences displayed on the T7 phage, and the peptide sequence with that of the negative and positive controls. NGS analysis showed the average net charge of the top-20 frequent sequences to approach neutral through the rounds of selection. Also, clone validation displayed above 10 times improved diffusivity of two of the neutral charged selected clone in comparison to the negative control (negative surface charge). However, the positive control (positive surface charge) exhibit 500 times stronger diffusing behavior in comparison to the negative control possibly because of the Donnan effect. In this study, we have selected two neutral charged hydrophilic peptide sequences with improved diffusivity through an in vitro tumor ECM model. We will further investigate the ability of the sequences to carry small molecule anticancer drug through the tumor ECM.

**Funding:** College of Pharmacy, University of Texas, Austin.

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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Abstract 31
INFLUENCE OF INHALATION FLOW ON PLUME GEOMETRY AND NASAL DEPOSITION OF NASAL SPRAYS

Daniel Moraga-Espinoza Zachary Warnken a, Amanda Moore a, Robert O. Williams IIIa, and Hugh D. C.Smytha*
a Department Of Molecular Pharmaceutics And Drug Delivery, College Of Pharmacy, The University Of Texas At Austin, Austin, Texas
b Escuela De Farmacia , Universidad Valparaiso, Valparaiso, Chile

Body of Abstract: Purpose: The ability to characterize the spray angle under flow conditions is of particular significance for nasal sprays as such devices are meant to be used under different inhalation regimens. Current in vitro techniques for assessing plume geometry, such as high-speed imaging or laser-assisted imaging, are unable to be performed under flow and do not account for the distribution of mass in the spray plume. With nearly all currently approved FDA nasal products instructing patients to inhale during actuation, an in vitro test that characterizes the plume angle under physiologically relevant inhalation flow rates would be useful if the results translate to deposition in the nasal cavity. The purpose of this study was to adapt the Plume Induction Port Evaluator (PIPE) apparatus developed for pressurized metered dose inhalers to be used for nasal sprays under flow.

Method: Mass median plume angles (MMPA) of four nasal spray products with increasing viscosities (HPMC 0 to 0.4%) were determined using PIPE apparatus in the absence and presence of flow. MMPAs were correlated to drug deposition within 3D printed nasal casts under the same flow rates. We evaluated three different inhalation regimens obtained from patient instructions of use in FDA approved products.

Results: Compared to no flow conditions, a significant reduction in the MMPA was detected by PIPE for the three formulations with the lowest viscosities. An increase in turbinate deposition was observed on the nasal casts when using flow and one of the nostrils was closed, except by the highest viscosity formulation. A nonlinear quadratic correlation between mass-based plume angles and turbinate deposition was observed when tested under the same flow rates.

Conclusion: We found that turbinate deposition increases when MMPA decreases. Similar quadratic correlation has been reported when testing nasal sprays with different plume angles in nasal casts. Therefore, based on these findings we proposed that changes detected in turbinate deposition are likely due to changes in plume geometry during inhalation. These results highlight the importance of testing nasal spray products taking in account the patients instructions of use.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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Purpose: Inflamed tissues are characterized by decreased pH, increased macrophages, and increased fenestrations between vascular endothelial cells, which may be exploited for targeted drug delivery. Our laboratory previously developed an acid-sensitive sheddable PEGylated nanoparticle for delivery to macrophages in tumors. Here, we modified this formulation to test the delivery of an anti-inflammatory drug to chronic inflammation sites.

Methods: We prepared nanoparticles using a method previously reported in our laboratory and chose betamethasone-21-acetate (BA) as a model anti-inflammatory drug. HPLC was used to determine the encapsulation efficiency of BA. We suspended our nanoparticles in a simulated biological medium at 37°C to measure in vitro stability. We confirmed the acid-sensitivity of BA-AS-M-NPs by pre-incubating nanoparticles in PBS (pH 6.8 or pH 7.4) before adding to J774A.1 macrophages. We also pre-incubated macrophages with mannose to confirm the functionality of mannose modification. To confirm the therapeutic activity of BA-AS-M-NPs, we stimulated macrophages with lipopolysaccharide (LPS) and treated with BA-AS-M-NPs, blank nanoparticles, free BA, or PBS and measured TNF-α expression. Similarly, to confirm that BA-AS-M-NPs can target chronically inflamed sites, we injected the footpad of C57BL/6 mice with LPS to induce inflammation. After 10 to 14 days, mice were treated with PBS, BA-AS-M-NPs, BA-AI-M-NPs, or free BA and were sacrificed 48 h later. We measured the BA content of the inflamed foot using HPLC.

Results: Our nanoparticles had an average size < 200 nm, polydispersity index (PDI) < 0.15, and zeta potential of -30 mV to -35 mV. The encapsulation of BA in the nanoparticles was greater than 50% and BA-AS-M-NPs were stable in a simulated biological medium. We confirmed that the acid-sensitivity of BA-AS-M-NPs significantly improved uptake at a decreased pH and that mannose-modification facilitated this uptake. BA-AS-M-NPs significantly reduced TNF-α levels in LPS-stimulated cells. In mice with LPS-induced chronic inflammation, BA-AS-M-NPs delivered more BA to the inflamed footpad after 48 h than BA-AI-M-NPs or free BA.

Conclusions: Here, we show that BA-AS-M-NPs target chronic inflammation sites and may be used to deliver anti-inflammatory therapies.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics
Abstract 34

COMBINATION OF KOLLI PHOR CS20 AND KOLLI PHOR RH40 TO IMPROVE RETENTION IN THE SKIN WHEN COMPARED TO INDIVIDUAL USE IN A HYDROPHILIC GEL


University of Texas at Austin, College of Pharmacy, Division of Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Purpose: The aim of this study was to analyze the drug skin retention properties of topical hydroxyethylcellulose hydrophilic gels (HHG) containing two surfactants alone or in combination. We compared three topical formulations containing a model compound (A) and hypothesize that combination of surfactants would enhance permeation across and into the skin

Methods: Compound A was dissolved in each HHG. Formulation 1 with Kolliphor CS20 (1%), Formulation 2 with Kolliphor RH40 (1%) and Formulation 3 (Kolliphor CS20 (1%) + Kolliphor RH40 (1%) were compared. Permeation across the skin was analyzed using excised fresh human skin in Franz diffusion cells (dose=0.1ml, n=6). The receptor fluid was filled with PBS (pH=7.4) and the skin was equilibrated for an hour at 37.0°C± 1.0°C. Samples were drawn from the receptor fluid at 0.5, 1, 2, 4, 6, and 12 hours. After 12 hours, the epidermis was separated from the dermis using a cryostat. The skin layers were weighed and methanol was used to extract the drug and to calculate the amount of drug per gram of skin. An HPLC method was used to analyze each sample

Statistical analysis was performed using a Wilcoxon Rank-Sum test for non-normally distributed data (α=0.05)

Results: The formulations were compared to the respective amount of drug present in the epidermis, dermis, and receptor fluid. In the epidermis, a higher retention of the drug was observed for Formulation 3 (1289.32 µg/g; IQR= 202.54) when compared to Formulation 2 (1018.72 µg/g; IQR= 826.34) and even more pronounced when compared to Formulation 1 (652.88 µg/g; IQR= 301.68). Although the difference between Formulation 2 and 3 was not statistically significant (p-value = 0.387), a statistically significant difference was observed when Formulations 1 and 3 were compared (p-value = 0.021). The same trend was observed in the dermis. In addition, the receptor fluid analysis showed that for Formulation 3 no Compound A was detected through 12 hours, except for one of the samples, whereas Compound A was found in detectable levels in the receptor fluid for Formulations 1 and 2

Conclusion: Skin permeation studies are known for their high variability, even if the same donor and area are used. Nevertheless, our study can still demonstrate that there was an enhancement in the amount of drug retained in the skin when both surfactants are used in combination

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics

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IDENTIFICATION OF BLOOD-BRAIN BARRIER PENETRATING PEPTIDES BY NEXT GENERATION SEQUENCING

Xiujuan “Sophie” Peng Alex Nguyen 2, Dhivya Arasappan3, Dennis Wylie3, Yanpeng Xi 2 Jasmim Leal1, Rana Ghosh1
1 Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, 2 College of Natural Science, 3 The Center for Computational Biology and Bioinformatics, University of Texas, at Austin

Body of Abstract: The blood brain barrier (BBB) impedes drug delivery of nearly 96% of small molecule drugs and all macromolecules into the brain parenchyma, which dramatically limits their therapeutic efficacy for brain diseases. Peptides are attractive carriers for transport across the BBB, as they offer the target specificity of larger proteins but at the size of small molecules for facile transport. Here, we present a strategy to use phage display to identify peptides that shuttle across the BBB and extracellular matrix molecules for effective transport. An M13 phage-presenting cyclic constrained 7-amino acid peptide library was panned against human-derived in vitro BBB model hCMEC/D3 cells for three sequential rounds using a modified pulse-chase assay. Eluates from this transcytosis assay were isolated and prepared for Illumina MiSeq next-generation sequencing. From the collected reads, Python and R were used to identify and analyze peptide sequences. From the top 20 most frequent clones after biopanning, the net charge was -1.18 – 0.93 (mean 0.18), and eight out of twenty clones were hydrophobic. Selected peptides that demonstrated enrichment throughout each round of biopanning were genetically engineered into M13 phage to validate their BBB shuttling function. From transport assays of the top four enriched clones, two of them possess significant BBB shuttling ability compared with scrambled peptide controls. Future work to elucidate the ability of peptides to penetrate and transcytose the BBB and diffuse through brain extracellular matrix will be discussed.

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Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics
Abstract 36

KETONE BODY ACTIONS AT LIGAND-GATED ION CHANNELS

**Natasha Pflanz** Anna W. Daszkowski
S. John Mihic

Department of Neuroscience, Division of Pharmacology and Toxicology, Waggoner Center for Alcohol & Addiction Research, Institutes for Neuroscience and Cell & Molecular Biology, University of Texas at Austin, Austin, Texas.

**Body of Abstract:** Ketogenesis is a metabolic process wherein ketone bodies are produced from the breakdown of fatty acids. In humans, fatty acid catabolism results in the production of acetyl-CoA which can then be used to synthesize three ketone bodies: acetoacetate, acetone, and β-hydroxybutyrate. Ketogenesis occurs at a higher rate in situations of low blood glucose, such as during fasting, heavy alcohol consumption, or situations of low insulin, such as in type I diabetes. Ketogenesis can also occur at a higher rate through a ‘ketogenic diet’ consisting of low carbohydrate and high fat intake. Studies have shown that this diet has therapeutic indications for the reduction of seizures in epileptic patients and for the suppression of alcohol withdrawal syndrome. However, the mechanisms underlying these therapeutic benefits remain unclear, with studies suggesting either a shift in energy production in the brain, effects on neurotransmitter production, or on the ability of ketone bodies to modulate ionotropic receptors. In this study we use two-electrode voltage clamp electrophysiology with Xenopus laevis oocytes to investigate the actions of ketone bodies on three ionotropic receptors: GABA, glycine, and NMDA receptors. We report that while physiological concentrations of acetone have little effect on inhibitory GABA or glycine receptors, β-hydroxybutyrate inhibits these receptors with low potency, which would lead to a decrease in GABA or glycine-mediated inhibition in vivo. Additionally, in contrast to previous studies, we find that both acetone and β-hydroxybutyrate act as potent inhibitors of the excitatory NMDA receptor (which in vivo would lead to less excitation by glutamate). Due to the role of hyperexcitability in the pathogenesis of epilepsy and alcohol withdrawal, the inhibitory actions of acetone and β-hydroxybutyrate at NMDA receptors may underlie the therapeutic benefit of a ketogenic diet for these disorders.

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Funding: NIH F31 DA042564

Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox
TRANSITION STATE DESTABILIZATION PROVIDES INSIGHTS INTO THE EFFECT OF GUANINE N7 ALKYLATION ON DNA REPLICATION

Aaron L Rozelle Yi Kou, Myong-Chul Koag, Seongmin Lee
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Body of Abstract: A wide variety of alkylating agents attack DNA to mainly produce N7-alkylguanine (N7-alkylG) adducts. Systematic studies on the effect of these major groove-positioned lesions on biological processes have been difficult due in part to the extreme chemical instability of the positively charged N7-alkylG. To gain insight into the effect of bulky N7-alkylG on DNA replication, we prepared N7-benzylguanine(N7bnG)-containing DNA via 2'-fluorine-mediated transition-state destabilization and evaluated the catalysis opposite the lesion using human DNA polymerase β (polβ) as a model enzyme for high-fidelity DNA polymerases. The presence of templating N7bnG almost completely inhibited dCTP insertion. The polβ-N7bnG:dCTP ternary complex structure showed an unusual conformation, where protein adopted an open conformation despite the formation of Watson-Crick N7bnG:dCTP base pair, explaining the dramatic decrease in the catalytic efficiency for correct insertion. The results indicate that polβ is highly sensitive to an aberration in the major groove and deters nucleotide insertion opposite bulky N7-alkylG adducts by adopting a catalytically incompetent conformation. Our results suggest that, although bulky alkyl groups at the guanine N7 may not alter base-pairing properties of guanine, the major-groove-positioned lesions can greatly impede nucleotidyl transfer by high-fidelity DNA polymerases.

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Class of Presentor: Graduate Student
COP Affiliation: CBMC
Abstract 38

DEVELOPMENT OF NEBULIZED CSP7 PEPTIDE FOR TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

**Sawittree Sahakijpijarn** Galina Florova2, Andrey A. Komissalov2, Sreerama Shetty2, Steven Idell2, and Robert O. Williams III1
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2The University of Texas Health Science Center at Tyler

**Body of Abstract:** Purpose: Carveolin-1 scaffolding domain peptide; CSP7 (FTTFTVT) is a novel candidate for the treatment of idiopathic pulmonary fibrosis which is a chronic disease with high mortality. Inhalation is an increasingly important route for delivery of biopharmaceuticals as it can deliver drug directly to the lungs and minimizes the drug’s systemic exposure. However, a major challenge of developing inhaled peptide formulations is peptide stability. In our present work, we developed nebulized peptide formulations and studied the stability of CSP7 for further preclinical and future clinical studies.

Methods: The solubility of CSP7 acetate in water was determined at different pH. Solution stability of CSP7 in buffer was studied after storage at different temperatures, following multiple freeze-thaw cycles and following exposure to mechanical agitation. The effect of nebulization on peptide aggregation was investigated. The CSP7 formulations with Dulbecco’s Phosphate Buffered Saline (DPBS) or Tris Buffered Saline (TBS) combined with bulking agents (mannitol, lactose and trehalose at molar ratios of 1:5, 1:70, 1:140, and 1:320) were developed as lyophilized formulations. Stability of reconstituted solutions and lyophilized cakes were studied.

Results: CSP7 acetate was more soluble in TBS than DPBS. CSP7 in the buffers were stable after storage at -20 °C, 2-8 °C and 25°C for short periods of time (i.e., 2-5 days) and after multiple (e.g., 5) freeze-thaw cycles at -20°C and -80°C. Lyophilized formulations (CSP7: Mannitol-1:140 molar ratio-DPBS, CSP7: Lactose-1:70 molar ratio-DPBS, CSP7: Trehalose-1:70 molar ratio-DPBS, CSP7: Mannitol-1:320 molar ratio-TBS, CSP7: Lactose-1:320 molar ratio-TBS, CSP7: Trehalose-1:320 molar ratio-TBS) exhibited acceptable cake appearance (e.g., smooth, homogeneous, and slightly little shrinkage) with low moisture content and short reconstitution time. The lyophilized CSP7 formulations were chemically stable for up to 3 months after storage 2-8 °C and 25 °C. The reconstituted solutions were stable for up to 3 days after storage at 2-8 °C and 25 °C. The nebulization did not affect the stability of peptide.

Conclusions: CSP7 peptide as the acetate salt was sufficiently stable in the solution state and solid state to be used for further preclinical and clinical studies.

**Funding:** This work was supported by Lung Therapeutics Inc.

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COP Affiliation: Pharmaceutics

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Abstract 39

OPIOID USE AMONG PATIENTS PRESENTING WITH MIGRAINE IN THE EMERGENCY DEPARTMENT

Sanket Shah, Karen Rascati, Carolyn Brown, Fawad Khan, Andrew Thach, Pooja Desai

Body of Abstract: Objectives: To describe opioid and other acute medication use in patients presenting to the emergency department (ED) with migraine.

Methods: This was a retrospective analysis using electronic medical records (EMRs) from Ochsner Health System, Louisiana from 2011 to 2016. Records were extracted for patients aged >18 with an ED visit coded for migraine and with at least six months baseline data. Descriptive statistics of patient demographics and acute medication use during the ED visit were summarized.

Results: Across 5,948 patients that met inclusion and exclusion criteria during the study period, a total of 15,153 unique ED encounters with a code for migraine were extracted. At least one acute prescription medication was administered in 9,204 (60.7%) of these encounters. Among ED visits for migraine where prescription medication was administered, nearly half (n=4,370/9,204, 47.5%) included at least one opioid. IV hydromorphone was administered in more than half (n=2,473/4,370, 56.6%) of these ED visits. In over one-fourth (n=1,144/4,370, 26.2%) of ED encounters in which an opioid was administered, patients were administered more than one dose of an opioid (i.e., either administration of a different opioid or administration of the same opioid with same or increased dose). Among non-opioid medications (e.g., antiemetics and non-opioid analgesics), antiemetics were the most frequently administered class, given in over one-third of ED (n=3,617/9,204, 39.3%) encounters where acute prescription medication was administered.

Conclusions: Despite best practice guidelines discouraging the use of opioids for migraine, opioids were administered in nearly half of the ED visits, pointing to potentially suboptimal care. Future research focusing on elucidating factors related to clinical decision making in the management of migraine in the ED and barriers to the utilization of effective preventive therapies is needed to reduce opioid overutilization.

Funding: Amgen Inc., Thousand Oaks, CA, USA

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TEMPORAL USE OF MEDICATIONS FOR THE MANAGEMENT/TREATMENT OF SICKLE CELL DISEASE

Nidhi Shukla  Dr. Jamie Barner

Body of Abstract: Background: Sickle cell disease is an inherited, chronic disorder characterized by a defect in the sickle cell hemoglobin gene. Symptoms include vaso-occlusive pain crises (VOC), acute chest syndrome, and leg ulcer resulting in frequent hospital admissions, emergency department and outpatient visits. About 100,000 Americans have SCD with annual mean expenditures ranging from $1.6 to 2.4 bn. Hydroxyurea is a current treatment to prevent the occurrence of SCD complications; but low adherence (74%) among patients negatively impacts effectiveness of the drug. Other therapies include opioids and non-opioids analgesics and antibiotics, with more than 80% patients prescribed analgesics. However, little is a known regarding the temporal treatment patterns of medication use in SCD.

Objective: The overall study goal is to understand temporal treatment patterns among SCD patients. The objectives are to: 1) describe medication use in terms of SCD index therapies and subsequent therapies and 2) determine if there are differences in the type of SCD index therapy by drug type and age group.

Methods: This is a retrospective secondary analysis of medical and prescription utilization using Texas Medicaid administrative claims data for patients diagnosed with SCD. The study includes patients aged 2 to 64 years with one inpatient SCD diagnosis and continuously enrolled in Medicaid. The study period will range from 1/1/2012–3/30/2016. Patients will be followed for 12 months after the index date. Study variables include drug type and age group, and two-way ANOVAs will be used to for statistical analysis.

Results: The feasibility analysis showed that there were N=9,211 unique Texas Medicaid patients with a SCD diagnosis between January 2012 and March 2015 without applying inclusion criteria. Descriptives such as patients’ age groups, gender, and proportion of patients of different age groups using different index drug types will be presented.

Conclusion: With SCD causing significant burden on patients and society and with the recent focus on the opioid epidemic, it is important to understand treatment patterns and health care utilization for SCD management enabling providers to develop strategies for addressing complications, incorporating preventive therapies, and increasing medication adherence.

Funding: n/a

Class of Presentor: Graduate Student
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Abstract 40
CHARACTERIZATION OF THE DIABETIC FOOT MICROBIOME BY SHOTGUN METAGENOMIC SEQUENCING: IMPLICATIONS FOR ANTIMICROBIAL STEWARDSHIP

James Shurko, Steven Dallas, Bryson Duhon, Jordan Meckel, Samantha Lee, Elijah Martin, Chiou-Miin Wang, Chun-Lin Lin, Nicholas Lucio, Nadeem Kirma, Grace Lee

1Pharmacotherapy Division, College of Pharmacy, UT Austin
2Pharmacotherapy Education and Research Center, School of Medicine, UT Health San Antonio
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4Department of Molecular Medicine, School of Biomedical Sciences, UT Health San Antonio

Body of Abstract: Background: Diabetic foot infections (DFIs) constitute the most common cause for diabetes-related hospitalization and lower extremity amputations. Currently, the association of the DFI microbiome and the development of complications is poorly understood. Further, current diagnostic methods are slow and in some cases do not detect all potential pathogens present in an infection. Metagenomics sequencing may offer an avenue to rapidly gain comprehensive information about causative pathogens in DFIs.

Objective: The objective of this study was to utilize metagenomics strategies to evaluate the impact of the DFI microbiome on the development of DFI related complications and to provide proof-of-concept of this approach for managing DFIs.

Methods: We profiled the microbiomes of thirty tissue specimens from patients with neuropathic plantar DFIs. Baseline characteristics, antimicrobial exposures, wound characteristics, and outcomes were collected. DFI complications were classified by ulcer deterioration, osteomyelitis, amputation, and DFI-associated death by 3 months after index DFI sample collection. Microbial 16s rRNA sequencing was conducted on the Illumina MiSeq instrument to assess relative abundance and the association of the microbiome with clinical features. Pathogens and antimicrobial resistance determinants (ARDs) were identified by shotgun metagenomics using the Nanopore MinION for 7 samples.

Results: Approximately 25% of patients experienced DFI complications. Tissue samples from patients who developed DFI complications had a higher relative abundance of Corynebacterium and Dermabacter while those that did not develop DFI complications had higher relative abundance of Streptococcus and Propionibacterium. The wound microbiomes differed significantly based on Hispanic ethnicity (p=0.004), HgA1C (p=0.04), and wound duration (p=0.04). Shotgun metagenomics correctly detected the pathogens found in culture and detected 8-32 ARDs per sample. The time to accurate classification was completed in <1hr.

Conclusion: Our data suggest Hispanic ethnicity, poor glycemic control, and duration of ulcer were associated with wound microbiomes. Additionally, metagenomics-based sequencing has the potential to offer a rapid and accurate strategy for detecting pathogens involved in DFIs.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmacotherapy

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Abstract 42

DEVELOPMENT AND BIOCHEMICAL CHARACTORIZATION OF INDOLINONE CORE SCAFFOLDS AS POTENT AND SELECTIVE INHIBITORS OF MELK.

Juliana M Taliaferro, Juhyeon Lee, Ram Edupuganti, Qiantao Wang, Matthew Harger, Eun Jeong Cho, Eric V. Anslyn, Pengyu Ren, and Kevin N. Dalby.

aDivision of Chemical Biology & Medicinal Chemistry, The University of Texas at Austin, TX 78712, USA. bThe Targeted Drug Discovery and Development Program, College of Pharmacy, The University of Texas at Austin, TX 78712, USA. cDepartment of Chemistry, The University of Texas at Austin, TX 78712, USA. dDepartment of Biomedical Engineering, Cockrell School of Engineering, The University of Texas at Austin, TX 78712, USA

Body of Abstract: Maternal embryonic leucine zipper kinase (MELK) is a member of the adenosine monophosphate kinase-related kinase (AMPK-RK) family that is highly expressed in several aggressive cancers such as triple negative breast cancer (TNBC) and glioblastoma multiforme (GBM). Much regarding MELK's functions both in normal and malignant tissues remains controversial, due in part to lack of a sufficiently specific inhibitor for use as an investigative tool. Following targeted kinase inhibitor library screening, we employed structure-guided design to develop two series of ATP-competitive indolinone derivatives based on the lead compound nintedanib (Ki = 5.6 ± 0.4 nM). The most potent derivatives of series 1 (17, Ki = 0.23 ± 0.04 nM) are slow-binding, with subnanomolar inhibition constants towards MELK. Based on molecular modeling studies, we designed Series 2 to target E93 near the ATP binding site and improved potency by 2-fold over 17 (b, Ki = 0.09 ± 0.02 nM). Combined steady state and pre-steady state kinetic characterization provides evidence that potent indolinone core inhibitors bind to MELK over at least three steps. Series 2 inhibitors display altered steady state and pre-steady state kinetic parameters compared to Series 1 inhibitors. Mutation to alanine (E93A) abrogates changes in steady state binding parameters, but not observable pre-steady state kinetic parameters. This data suggests contact with E93 minimally contributes to preliminary binding steps, but is important for later binding steps and overall potency. Series 2 improves upon selectivity against tyrosine kinase targets of nintedanib (b, KiFGFR1/KiMELK = 200, KiVEGFR1/KiMELK = 98). We also add to the growing evidence that OTS167 is nonselective and therefore an inappropriate means to assess MELK activity in mitotic MDA-MB-231 cells. These studies suggest that continued elaboration of the indolinone scaffold will furnish much needed MELK-selective inhibitors with potential for use as molecular biology tools as well as development in preclinical models of TNBC and other cancers.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: CBMC

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Body of Abstract: The objective of this study was to develop suitable extraction conditions for the determination of Apremilast in mouse plasma, brain, and liver tissue for measurement by high-performance liquid chromatography (HPLC). Method development was performed using a Dionex Ultimate 3000 HPLC with UV detector. The separation employed a gradient on an Eclipse Plus C18 column (3.0 x 150 mm, 3.5 µm) with an EC-18 guard column (3.0 x 5.0mm, 2.7 µm), at 30°C, 230nm, and a 15 minute run time. The ternary gradient mobile phases were 0.1% phosphoric acid in water (v/v), acetonitrile (25 to 75%), and methanol (hold at 10%), at a flow rate of 0.6 mL/min. The method evaluation included system suitability, linearity, selectivity, accuracy, and precision. Several salts were screened for use in the salting-out assisted liquid-liquid extraction (SALLE) procedure. SALLE included adding acetonitrile to sample followed by concentrated salt solution, which induced separation of aqueous and organic phases. The acetonitrile layer was transferred, evaporated, and reconstituted in diluent. Naproxen was used as the internal standard.

Initial SALLE selectivity screening was performed by spiking water; subsequent evaluation was performed by spiking blank mouse plasma, brain, or liver. Selectivity was optimized by use of magnesium chloride for plasma, an ammonium sulfate-sodium chloride mixture for brain tissue, and a double-extraction using both ammonium sulfate-sodium chloride, and magnesium chloride for liver tissue. System suitability results included Apremilast peak area RSD ≤ 5.0%, and retention time RSD ≤ 0.5%, R2 ≥ 0.99, and average tailing factor ≤ 1.3. Selectivity was demonstrated by extracting unspiked mouse plasma, brain, and liver. Calibration was performed by spiking plasma (0.5-500 ng/100 µL), brain (0.6-30 ng/100 mg), and liver (1.5-3000 ng/100 mg), in triplicate, at six or more levels of Apremilast. The method was suitably precise, linear, and accurate for assay analysis (R2 ≥ 0.99, RSD 0.5 -4.4% in plasma, 1.3-15% in brain, and 0.5-13% in liver). A selective, sensitive, accurate, and precise bioanalytical method was successfully developed for assay of Apremilast in mouse plasma, brain, and liver tissue using SALLE and HPLC-UV. Results indicate the method is suitable for use in a biodistribution study of Apremilast in mice.

Funding: n/a

Class of Presentor: Graduate Student
COP Affiliation: Pharmaceutics
PHARMACIST AND PHYSICIAN REPORTING OF PALBOCICLIB IN THE FDA ADVERSE EVENT REPORTING SYSTEM

Chengwen Teng Obiageri Obodozie-Ofoegbu, Lindsey Groff, Victor Encarnacion, Huda Razzack, Bradi Frei, and Christopher Frei
The University of Texas at Austin College of Pharmacy and University of Texas Health Science Center School of Medicine, San Antonio, TX

Body of Abstract: Background: The FDA Adverse Event Reporting System (FAERS) contains adverse event reports from pharmacists, physicians, consumers, lawyers, and other health professionals. No published studies to date have compared pharmacist and physician reporting in the FAERS for palbociclib.

Objective: The objective of this study is to compare the adverse event reporting of palbociclib between pharmacists and physicians.

Methods or Procedures: Data were obtained from the FAERS and were processed and analyzed by Microsoft Access 2016, Microsoft Excel 2016, and JMP Pro 13. Adverse events for palbociclib reported to the FDA from January 1, 2015 to September 30, 2017 were extracted from the dataset. The proportions of adverse events associated with death and hospitalization, as reported by pharmacists and physicians, were compared with chi-square tests. P-values less than 0.05 were considered to be statistically significant.

Results: Overall, there were 10,140 adverse events reported in the FAERS for palbociclib during the study period: 2,655 by pharmacists and 1,880 by physicians. Physicians were significantly more likely to report death as an adverse event associated with palbociclib than were pharmacists (9.9% vs. 4.7%, p < 0.0001). Physicians and pharmacists were equally likely to report hospitalization as an adverse event associated with palbociclib (10.1% vs. 9.8%, p = 0.8).

Conclusions: Physicians were more likely to report death as an adverse event associated with palbociclib than were pharmacists. It is possible that physicians are more likely to encounter patients in urgent and emergent care situations, than are pharmacists. Further research is needed to explain the underlying cause.

Disclosures: The authors of this presentation have nothing to disclose.

Funding: n/a

Class of Presenter: Graduate Student
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Abstract 45

SHORT-TERM TOXICITY STUDY OF 4-(N)-DOCOSAHEXAENOYL 2’, 2’-DIFLUORODEOXYCYTIDINE, AND ITS ANTITUMOR ACTIVITY IN A MOUSE MODEL OF LEUKEMIA

Solange Valdes Youssef Naguib, Zhengrong Cui. UT Austin College of Pharmacy, Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Introduction: 4-(N)-docosahexaenoyl 2’, 2’-difluorodeoxycytidine (DHA-dFdC) is a novel compound synthesized by conjugating docosahexaenoic acid (DHA) with 2’, 2’-difluorodeoxycytidine (dFdC). Previously we reported a strong and potent antitumor activity against NCI-60 human cancer cell lines, especially against renal, central nervous system, and leukemia cancer cell line.

Rationale: The purpose of this study is to evaluate the short-term toxicity of DHA-dFdC in healthy mice when administered intravenously and evaluated its antitumor activity at or below its repeat-dose maximum tolerated dose (RD-MTD) in a leukemia model.

Method: To evaluate the toxicity of DHA-dFdC a short-term toxicity study was designed. Healthy DBA/2 mice received intravenous (i.v.) injection of DHA-dFdC on a repeated-dose schedule (i.e. injections on day 0, 3, 7, 10, and 13). DHA-dFdC solution was injected i.v. to the mice at various doses: 70 mg/kg, 60 mg/kg, 53 mg/kg, 50 mg/kg, and 0 mg/kg (vehicle). Another group of healthy mice were injected i.v. with three doses of DHA-dFdC at 100 mg/kg on days 0, 3, and 5 (i.e. a lethal-RD) to evaluate the effects of high dose of DHA-dFdC in main organs and blood and serum parameters. The body weight of mice was recorded two or three times a week. At the end of the study, major organs (i.e. heart, liver, spleen, kidney, lung, and pancreas) of mice, which received RD-MTD and lethal-RD of DHA-dFdC were harvested and weighed, and blood samples were collected for blood and serum parameter analyses. Finally, DHA-dFdC was injected i.v. into female DBA/2 mice with syngeneic L1210 mouse leukemia cells to evaluate its efficacy at or below RD-MTD.

Results: The RD-MTD of DHA-dFdC was 50 mg/kg when given by i.v. injection in a spaced schedule. At lethal-RD, DHA-dFdC decreases the body weight of mice, and also decreases the spleen and liver weight. The main blood parameters affected by lethal-RD are white blood cells, lymphocytes, eosinophils, and neutrophil segmented. Finally, DHA-dFdC prolonged the survival in leukemia mouse model at or below its RD-MTD.

Conclusion: DHA-dFdC has dose-limiting toxicity, affecting mainly spleen at a lethal dose. At or below its RD-MTD, DHA-dFdC has a potent antitumor activity against leukemia mouse model.

Funding: National Institute of Health grant (CA179362) and Becas-Chile scholarship from the government of Chile.

Class of Presentor: Graduate Student
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STRUCTURAL BASIS FOR THE BYPASS OF THE MAJOR OXALIPLATIN-DNA ADDUCT BY HUMAN DNA-POLYMERASE H

Caroline Kate Vilas, Hala Ouzon-Shubeita Meghan Baker, Myong-Chul Koag, Seongmin Lee
Division of Chemical Biology and Medicinal Chemistry, College of Pharmacy,
The University of Texas at Austin, Austin, TX 78712, USA

Body of Abstract: The chemotherapeutic agent oxaliplatin contains a bulky diaminocyclohexane (DACH) moiety, which produces (DACH)Pt-GpG intrastrand cross-links that impede transcription and kill cancer cells. Another platinum-based anticancer drug, cisplatin also induces DNA crosslinking, forming cisplatin-DNA adducts. Differential recognition of oxaliplatin- and cisplatin-DNA adducts by various proteins, such as mismatch repair proteins and DNA polymerases, contributes to distinct cytotoxicities of these platinum-based drugs. There are several published structures of DNA polymerase bound to cisplatin-DNA adducts; however, a structure of DNA polymerase in complex with oxaliplatin-DNA adducts has not yet been reported, limiting our understanding of molecular mechanisms that underlie disparate processing of platinum drug-DNA adducts by DNA polymerases. Here, we report two crystal structures of human DNA polymerase (Pol) incorporating dCTP opposite 3'G and 5'G of the (DACH)Pt-GpG intrastrand cross-link. The 3'-insertion structure differs from the equivalent Pol-cisplatin-GpG structure in conformations of Pt-GpG and the catalytically important Arg61. The 5'-insertion structure shows only the nucleotide-binding metal ion in the active site, which is in contrast to the observation of both nucleotide-binding and catalytic metal ions in the corresponding Pol-cisplatin-GpG structure. This finding explains inefficient catalysis opposite 5'G of (DACH)Pt-GpG. Taken together, our results uncover the structural basis for differential processing of oxaliplatin- and cisplatin-induced DNA lesions by a translesion synthesis DNA polymerase.

Funding: NIH R01 ES26676

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COP Affiliation: CBMC

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Abstract 47

3D-PRINTED NASAL CASTS FOR ANALYZING THE EFFECT OF PERSONALIZED ADMINISTRATION ANGLES ON THE TARGETING OF NASAL SPRAY DEPOSITION IN PEDIATRICS AND ADULTS

Warnken, Zachary Hugh D.C. Smyth, Robert O. Williams III
University of Texas at Austin College of Pharmacy, Molecular Pharmaceutics and Drug Delivery Division

Body of Abstract: Previous reports assessing nasal spray deposition are generally limited to studies performed in a single nasal cast. Due to large variability in nasal cavity structure, the results from a single nasal cast may not translate to the general population. The purpose of this study was, firstly, to assess nasal spray deposition in five pediatric and five adult casts with varying formulations and administration angles and, lastly, to find and utilize patient-specific administration angles to improve turbinate targeting and reduce the variability between individual casts.

Nasal casts based on CT-scans were 3D-printed for studying deposition. Five nasal spray formulations containing cromolyn sodium and HPMC, as model drug and viscosity enhancer, were tested to compare differences in deposition with changing plume angle in the “comfortable use position” for nasal sprays. The effect of administration angles on turbinate targeting was assessed using the 0.8% HPMC cromolyn sodium formulation. From the results of this study, the region for maximized turbinate deposition in each individual cast was found and used in a central composite design of experiments (DOE) to ascertain the optimized angle in each individual cast.

No significant differences in deposition were found for any particular formulation at this administration angle. Decreasing the administration angle from 75 to 30 degrees corresponded with an increase in the percentage of drug deposited in the turbinate region. The highest turbinate deposition was found for an angle of 30 degrees.

A DOE was used to optimize the administration angle for maximal turbinate deposition in each nasal cast. There was a significantly greater percentage of cromolyn sodium in the turbinate region with the use of the optimized personalized angles compared to that found for the 30-degree angle, 90.5% ± 8.3 versus 72.9% ± 12.4 respectively (p-value < 0.05).

By utilizing personalized administration parameters, the targeting efficiency of nasal sprays is significantly increased and, in the case of the pediatric population, the variability could be decreased. While there is a clear benefit to personalized nasal drug delivery for turbinate deposition, further research is required to see if these parameters can be device-controlled for patients and if other regions can be effectively targeted.

Funding: Pre-Doctoral Fellowship from PhRMA Foundation

Class of Presenter: Graduate Student
COP Affiliation: Pharmaceutics

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SYSTEMIC DEPLETION OF L-METHIONINE WITH AN ENGINEERED HUMAN ENZYME FOR MELANOMA TREATMENT

Carly Wilder  John DiGiovanni

Body of Abstract: Metastatic melanoma is an aggressive form of cancer responsible for the majority of skin cancer related deaths. While treatment for metastatic melanoma has improved in recent years with the introduction of targeted and immunotherapies, the five year survival rate for metastatic melanoma is only 20%. This project introduces an alternative treatment option, an engineered enzyme called human methionine-gamma-lyase (hMGL). The hMGL enzyme works by degrading extracellular L-methionine resulting in cancer cell starvation while non-cancerous cells experience little to no adverse effects. The hypothesis evaluated in this ongoing project is that the systemic depletion of L-methionine using hMGL will provide significant benefits for the treatment of melanoma. To evaluate the hypothesis, the effects of hMGL on cell survival, cell cycle inhibition, pathways that inform the mechanism of interest, and potential synergistic combinations with thioredoxin reductase inhibiting compounds were evaluated in melanoma cell lines. Preliminary data demonstrate that melanoma cell survival is inhibited and cell cycle arrest occurs with hMGL treatment of melanoma cell lines. Additionally, the oncogenic STAT3 signaling pathway is inhibited while autophagy (as assessed by LC3-II levels) increases with hMGL treatment. Furthermore, there was a synergistic combinatorial effect on melanoma cell survival with hMGL and the thioredoxin reductase inhibitors ethaselen and auranofin. Future directions include additional research on the mechanisms of action and the evaluation of hMGL against melanoma tumor growth in vivo with and without the addition of thioredoxin reductase inhibitors. Research funded by CPRIT RP180590.

Funding: CPRIT RP180590

Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox
NASAL ALUMINUM (OXY)HYDROXIDE ENABLES ADSORBED ANTIGENS TO INDUCE SPECIFIC SYSTEMIC AND MUCOSAL IMMUNE RESPONSES

Haiyue Xu  Tinashe B. Ruwona, Sachin G. Thakkar, Yanping Chen, Mingtao Zeng, Zhengrong Cui

Body of Abstract: Purpose The present study is designed to assess the feasibility of repurposing aluminum salts in injectable vaccines as nasal mucosal vaccine adjuvants.2028

Methods Using Alhydrogel®, the international scientific standard of aluminum (oxy)hydroxide gels, monophosphoryl lipid A (MPLA) as a positive control, and ovalbumin (OVA) or 3×M2e-HA2, a synthetic influenza virus fusion protein as antigens, we immunized BALB/c mice intranasally three times, two weeks apart. Two weeks after the last immunization, mice were euthanized. Blood sera and splenocyte were isolated. Systemic immune responses including anti-mouse IgG, IgG1 or IgG2a were detected in the blood sera, and mucosal immune responses including anti-mouse IgA were detected in the nose wash and bronchoalveolar lavage (BAL) using ELISA. The levels of cytokines, IL-4 and IFN-γ, released by splenocytes after in vitro stimulation were also determined.2028

Results We showed in a mouse model that when dosed intranasally, aluminum (oxy)hydroxide can enable antigens adsorbed on it to induce antigen-specific immune responses in both serum samples (e.g. specific IgG) and nasal and lung secretions (i.e. specific IgA) in all immunized mice. For the OVA antigen, nasal OVA/Alhydrogel® induced stronger specific IgA responses than the OVA alone in the nasal wash and BAL samples of all the immunized mice. Nasal OVA/Alhydrogel® was more immunogenic than nasal OVA alone in inducing OVA-specific serum IgG1 as well. The splenocytes from mice nasally immunized with OVA/Alhydrogel® released IL-4 after in vitro stimulation with OVA, whereas those immunized with OVA alone did not. For the 3×M2e-HA2 antigen, 3×M2e-HA2/Alhydrogel® also induced specific IgA responses in the nasal wash and the BAL samples of all the immunized mice, while nasal 3×M2e-HA2 alone did not. Nasal 3×M2e-HA2/Alhydrogel® induced strong specific serum IgG antibodies as well (p < 0.05 vs. 3×M2e-HA2 alone).2028

Conclusion Alhydrogel® enabled the OVA and 3×M2e-HA2 antigens to induce specific systemic and mucosal immune responses. Rerouting insoluble aluminum salt-based adjuvants such as Alhydrogel® in injectable vaccines may represent a viable approach for (nasal) mucosal vaccine adjuvant discovery.

Funding: US. National Institute of Allergy and Infectious Diseases (AI105789), Alfred and Dorothy Mannino Fellowship in Pharmacy at UT Austin, National Natural Science Foundation of China (81460454) and the Inner Mongolia Natural Science Fund (2014ZD05)

Class of Presentor: Graduate Student
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AMBIENT STABILITY OF SHELF FREEZE DRIED BACTERIOPHAGE POWDERS

Yajie Zhang1, Xiujuan Peng1, Hairui Zhang1, Alan B. Watts1,2*, Rana Ghosh1*

1. Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, University of Texas at Austin, Austin, TX, USA
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Body of Abstract: Purpose: Alternative treatments for bacterial infections are urgently needed due to the emergence and growth of multidrug resistance to many antibiotics. Bacteriophage (also called phage) therapy has re-emerged a promising treatment to circumvent the challenges of antibiotics. However, due to their complicated structure, phage need to be formulated carefully to retain their stability and viability. Our work screened and optimized processing and formulations of phage powders and investigated their stability under ambient (22-25°C) conditions.

Method: A model phage, M13, was formulated with trehalose, mannitol, sucrose and/or PEG6000, respectively and shelf freeze-dried in different conditions. Bacteriophage viability was examined by standard plaque assay to assess phage stability. Phage powders were further characterized using Karl Fischer, Transmission Electron Microscopy, polarized light microscope and X-Ray Diffraction.

Results: Phage formulated with 2% trehalose or sucrose retained greater activity (higher titer) compared with mannitol and PEG formulations for both immediate and long-term storage. An additional 1 log titer preservation was observed upon reduction of the dehydrating stress during lyophilization process. Trehalose and sucrose were stabilized in amorphous state whereas mannitol was crystalline in lyophilized powders. Measured moisture content (3.58% in Trehalose and 2.2% in PEG) was demonstrated to have a positive correlation with viability of phage (7.5 log and 5.4 log titer in Trehalose and PEG, respectively).

Conclusion: The disaccharides trehalose and sucrose are attractive excipients to stabilize and retain viability of phage during shelf freeze-drying and storage in ambient conditions. Interestingly, residual moisture has a positive impact on preservation of phage activity.

Funding: The University of Texas at Austin College of Pharmacy

Class of Presentor: Graduate Student
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DNA POLYMERASE BETA MUTATION DRIVES INFLAMMATION THROUGH CHROMOSOMAL INSTABILITY

Shengyuan Zhao Jenna Rozacky, Alex Klattenhoff, Chad McCants, Christopher Chu, Megha Thakur, Dawit Kidane
Division of Pharmacology and Toxicology, College of Pharmacy
Dell Pediatric Research Institute, University of Texas at Austin, Austin-USA

Body of Abstract: Introduction: DNA polymerase beta (Pol β) is a key enzyme in mammals to repair DNA lesions produced from oxidation or alkylation via its role in the base excision repair (BER) pathway. The dRP lyase domain of Pol β is responsible for removing the 5’ phosphate group, which prepares the damaged DNA for further processing by the polymerase activity of Pol β. Previously, we have shown that the dRP lyase function of Pol β is critical for the maintenance of DNA replication fork stability and prevention of DNA double-strand breaks (DSBs).

Hypothesis: To test the hypothesis that the human gastric cancer associated variant of Pol β (L22P) induces genomic instability driven inflammation, accelerating carcinogenesis in mice.

Methods: We constructed a Pol β L22P conditional knock-in mouse model, and evaluated nuclei abnormality using immunofluorescence. Further, we tested the activation of cytosolic DNA sensor cGAS-STING (stimulatory interferon gamma) pathway arising from genome instability with western-blot and qRT-PCR.

Results: We found that mitotic progression with unrepaired DSBs resulted in micronuclei. Further, we observed that GFP-cGAS localizes with micronuclei arising from genome instability and activates the STING/TBK (Tank binding kinase-1)/IRF3 (interferon regulatory factor-3) axis to trigger inflammatory responses.

Conclusion: Our data suggest that micronuclei in L22P cells promote a STING mediated inflammatory response. Thus, our results reveal a previously uncharacterized role of Pol β in prevention of mitotic chromosomal segregation defects to suppress inflammatory responses, placing Pol β at the hub of new interconnections between aberrant BER and chromosome driven immune responses.

Funding: Class of Presentor: Graduate Student
COP Affiliation: Pharm/Tox

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AN INTERIM ANALYSIS OF THE UTILITY OF PHARMACOGENOMICS FOR REDUCING ADVERSE DRUG EFFECTS (UPGRADE) TRIAL: A CASE FOR THE NECESSITY OF PHARMACOGENOMIC TESTING IN THE HISPANIC POPULATION.

Cesar Orlando Bañuelos Jim Koeller, University of Texas Health Science Center at San Antonio, Pharmacotherapy Division

Body of Abstract: Background: Pharmacogenomics (PGx) allows for the optimization of pharmacotherapy utilizing knowledge of genetic polymorphisms within the human genome. Most PGx research has focused on Caucasians with minimal emphasis on the PGx of ethnic minorities.

Objective: The objective of this study was to describe specific genetic polymorphisms among major CYP450s & VKORC1 alleles and to evaluate the effect of PGx-based pharmacotherapy adjustments on patient outcomes within the Hispanic and Caucasian populations.

Methods: The UPGRADE trial is an ongoing, prospective, multi-center study analyzing the effect of PGx and patient outcomes. This retrospective analysis consisted of 27,272 participants enrolled in the UPGRADE trial from 04/01/2014 through 07/31/2015. The study involved 4 phases: (1) screening, (2) a 90-day pre-PGx testing follow up, (3) PGx testing with relevant pharmacotherapeutic recommendations, and (4) a 90-day post-PGx testing follow up. Participants continued their current medication regimen unless altered in phase 3. Frequency of hospitalizations, adverse drug reactions (ADR), and emergency department visits were evaluated after each 90-day period.

Results: There were multiple differences in the expression of major CYP450s between Hispanics and Caucasians. The largest difference was in the rate of CYP3A5 genotype *3A/*3A expression between Hispanics and Caucasians (53% vs 70%, p <0.0001). There were also higher proportions of CYP3A5 poor (*3A/*6) and extensive (*1A/*1A) metabolizers among Hispanics compared to Caucasians. Tacrolimus is a major substrate of CYP3A5. Of 18 Caucasian and 8 Hispanic patients who received tacrolimus in the cohort, all 18 Caucasian patients expressed an intermediate metabolizer genotype (*3A/*3A). Whereas, the 8 Hispanic patients exhibited a wide range in genotypes. Prior to PGx-based pharmacotherapy adjustments, there was a trend towards increased adverse drug reactions (ADRs) in Hispanic tacrolimus patients compared to the Caucasian patients (29% vs 11%, p=0.28). After PGx-based adjustments, the frequency of ADRs decreased by 89% in the Caucasian group and 81% in the Hispanic group.

Conclusion: CYP3A5 genetic testing along with genotype-guided dosing could offer a safer method of treating Hispanic patients receiving CYP3A5 substrates.

Funding: n/a

Class of Presenter: Pharmacy Student
COP Affiliation: Pharmacotherapy
Abstract 53

NATIONAL OUTPATIENT GASTRIC ACID SUPPRESSANT PRESCRIBING IN THE UNITED STATES BETWEEN 2009 AND 2015

Hannah Bustillos Leer, Kelsey, Reveles, Kelly
, University of Texas at Austin College of Pharmacy Pharmacotherapy Education & Research Center, The University of Texas Health Science Center San Antonio

Body of Abstract: Introduction: Gastric acid suppressants (GAS), namely proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA), are indicated for gastroesophageal reflux disease (GERD). Once initiated, they are often used chronically without clear therapeutic intent. While generally well-tolerated short-term, long-term use has been associated with infection, bone fractures, and nutrient malabsorption. Despite these associations, it is unknown if GAS prescribing has changed in recent years.

Objective: To investigate national trends in GAS use over a 7-year period.

Method(s): This was a cross-sectional study using the data from the National Ambulatory Medical Care Survey (NAMCS), a national probability sampling of outpatient physician office visits conducted by the Centers for Disease Control and Prevention. Data weights were used to derive national estimates. GASs included any prescription for a PPI or H2RA documented during the outpatient visit. Use was calculated as the number of prescriptions per total outpatient visits per year. Demographics and regional prescribing were compared between GAS users and nonusers. The Wilcoxon rank-sum test was used to compare age between GAS users and non-users, while the chi square test was used to compare sex and race. The overall proportions of specific PPIs and H2RAs prescribed were also observed.

Result(s): These data represent 6.8 billion outpatient visits between 2009 and 2015, of which nearly 600 million (8.8%) had documented GAS use. The median (IQR) age of GAS users was 62 (50-73) and non-GAS users was 49 (25-65). GAS users were predominantly female (60.4%) and White (85.2%). H2RA use was steady (average of 1.66% of all outpatient prescriptions) from 2009 to 2015. PPI use decreased from 7.8% in 2009 to 6.5% in 2012, and then increased to 8.4% in 2015. H2RA and PPI use were comparable among all four geographic regions, with PPI use slightly higher in the Midwest (8.3%). Ranitidine was the most commonly used H2RA (62.0%) and omeprazole the most common PPI (52.1%).

Conclusion(s): GAS were commonly prescribed in outpatients from 2009 to 2015. PPI use steadily increased after 2012. Further data analysis will assess appropriateness of GAS prescribing among US outpatients.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Other

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HMGB3 AS A NOVEL MOLECULAR TARGET TO INDUCE CISPLATIN SENSITIVITY IN CHEMORESISTANT OVARIAN CANCER CELLS

Kailee Gaines, Anirban Mukherjee, Ph.D., UT Austin College of Pharmacy, Division of Pharmacology and Toxicology; Van Huynh, UT Austin College of Pharmacy, Division of Pharmacology and Toxicology; Karen Vasquez, Ph.D., UT Austin College of Pharmacy, Division of Pharmacology and Toxicology

Body of Abstract: Ovarian cancer is the fifth most common cause of cancer-related deaths in women. Current ovarian cancer survival rates are poor, partly due to the frequent development of resistance to chemotherapy (e.g. cisplatin). Once resistance develops in ovarian tumors, further response to chemotherapy is minimal and subsequent survival is limited to 9-12 months for the majority of patients. Considering the drastic reduction in survival in patients with chemotherapy-resistant cancer, determining mechanisms to overcome this resistance is of great importance to human health. In this study, we investigated the non-histone architectural protein High Mobility Group Box 3 (HMGB3) as a novel target to induce platinum sensitivity in resistant ovarian cancer cells. Our studies reveal that HMGB3 plays a role in the processing of chemotherapeutic lesions, such as DNA double-strand breaks (DSBs) and DNA interstrand crosslinks (ICLs) formed by cisplatin in human cancer cells. Therefore, we hypothesized that suppression of HMGB3 expression would modulate DSB and/or ICL processing, ultimately leading to decreased survival of ovarian cancer cells following cisplatin treatment. To test this, we depleted HMGB3 in cisplatin-resistant human ovarian cancer cells (A2780cis) via an siRNA approach and subsequently treated the cells with cisplatin. Cisplatin-sensitive ovarian cancer cells (A2780), non-transfected A2780cis cells, as well as A2780cis cells transfected with non-targeted siRNA were treated with cisplatin as controls. Untreated, non-transfected A2780cis and A2780 cells were also seeded to provide untreated controls. Cells were incubated for a 2 week period, and resulting colony formation was assessed by staining colonies with crystal violet. HMGB3 depletion was assessed by western blots to be ~89% in cisplatin-resistant A2780cis cells, which showed a 55% mean reduction in colony formation following cisplatin treatment compared to HMGB3 expressing cisplatin-resistant A2780cis cells receiving identical treatment. Taken together, our results suggest that inhibition of HMGB3 may reduce cisplatin resistance in ovarian cancer cells, increasing tumor susceptibility to cisplatin treatment.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharm/Tox

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FACTORS RELATED TO THE LACK OF PRE-EXPOSURE PROPHYLAXIS (PREP) UPTAKE IN MEN WHO HAVE SEX WITH MEN (MSM)

Austin Green, BCS 1 Carolyn Brown, PhD 1
1UT Austin College of Pharmacy, Health Outcomes and Pharmacy Practice Division

Body of Abstract: Introduction: Pre-Exposure Prophylaxis (PrEP) is available as a one pill, once per day medication to prevent HIV infection alongside conventional protection such as condoms, but its use among high-risk populations has been low. While little research has been conducted regarding the lack of uptake of PrEP in the high-risk MSM population, early qualitative studies suggest a variety of educational and personal factors can contribute to low PrEP use.

Objectives: To analyze reasons for low PrEP use in the MSM population and to determine if reasons vary with demographic variables.

Method: A brief survey, consisting of demographic variables and five factors found to contribute to lack of PrEP uptake, was distributed to participants who were MSM and self-reported as HIV negative and not on PrEP. PrEP uptake items were measured on a 1 to 7 scale (1=Strongly disagree and 7=Strongly agree). Participants who consented completed the survey. As part of this on-going study, 26 surveys have been distributed to date. Using STATA 15IC, data were analyzed descriptively (mean, standard deviation, frequencies) and inferentially (t-test and ANOVA for comparisons).

Results: A total of 26 surveys were analyzed. Overall, participants mostly disagreed about: their uncertainty of PrEP's effectiveness (Mean=2.42, SD=1.24), their ability to adhere to PrEP (Mean=3.12, SD=1.40), the appropriateness of PrEP given their perceptions of not being at high risk for contracting HIV (Mean=3.62, SD=1.83), PrEP's inability to prevent other STIs (Mean=3.38, SD=1.77), and moral reasons for not being on PrEP (Mean=2.81, SD=1.39). Race/ethnicity was significantly related to beliefs about the appropriateness of PrEP given estimated lower risk for contracting HIV (p=0.0065).

Conclusion: These preliminary results suggest that individuals' strongest reason for not using PrEP is that they do not believe its use is appropriate given their estimates of not being at high risk for contracting HIV and this reason differed by race/ethnicity. Additional data may reveal other significant correlates.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: HOPP
A CLOSER LOOK AT OPPORTUNITIES AND EXPERIENCES FOR PHARMD STUDENTS TO PURSUE LEADERSHIP

Emma Gugala Rochelle Roberts, UT Austin College of Pharmacy

Body of Abstract: Rationale: The Accreditation Council for Pharmacy Education (ACPE) Standard 4.2 states, “the graduate is able to demonstrate responsibility for creating and achieving shared goals, regardless of position.” Previous literature on leadership development in a PharmD program has determined motivations for students seeking leadership positions (Moore and Ginsburg, 2017), and competencies for student leadership development (Janke, Traynor, and Boyle, 2013). The purpose of this research is to determine how, when, and where current P3 students at the University of Texas at Austin College of Pharmacy (UTCOP) develop leadership skills.

Methods: An analysis of the current membership of student organizations and student initiatives at the UTCOP was conducted to identify leadership positions available and any other patterns. Following that, an anonymous survey was distributed to the P3 students to assess their individual leadership development and gain information beyond organization membership data. Due to low response rate, 15 semi-structured interviews were performed to gain deeper insight to specific and previously unrecognized opportunities for leadership development.

Results: Of the 377 P1-P3 students, 343 are involved in at least one organization, and 236 hold at least one leadership position. Survey data showed 82%-97% of the 33 P3 respondents gained experience meeting various leadership competencies at least “a moderate amount” during their time in the PharmD program. Interviewees overall described different types of leaders, pursued leadership opportunities to varying degrees, and cited a wide range of leadership opportunities from within lab courses to high-level committee work for a national organization. In addition, those opportunities were impactful when they could develop new skills for their own professional development or initiate a project and witness the positive effects it has on others.

Conclusion: Complete results could be shared with Pharmacy Council as well as UTCOP administration to help determine if students can be informed about the breadth and depth of leadership opportunities available to them, in hopes that all students could benefit from some kind of leadership experience.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Other
Abstract 57

SOLUTION STRUCTURE OF THE MYCOBACTERIUM TUBERCULOSIS ESXG-ESXH COMPLEX: FUNCTIONAL IMPLICATIONS AND COMPARISONS WITH OTHER M. TUBERCULOSIS ESX FAMILY COMPLEXES.

Dariush Ilghari, Kirsty L. Lightbody, Vaclav Veverka, Lorna C. Waters, Frederick W. Muskett, Philip S. Renshaw and Mark D. Carr.
From the Department of Biochemistry, University of Leicester, Henry Wellcome Building, Leicester LE1 9HN, United Kingdom

Body of Abstract: Introduction and Rational: Mycobacterium tuberculosis is the primary causative agent of human tuberculosis and one of the oldest pathogens known to man. M. tuberculosis encodes five type VII secretion systems that are responsible for exporting a number of proteins, including members of the Esx family, which have been linked to tuberculosis pathogenesis and survival within host cells. The gene cluster encoding ESX-3 is regulated by the availability of iron and zinc, and secreted protein products such as the EsxG·EsxH complex have been associated with metal ion acquisition.

Method: In this study, EsxG and EsxH were expressed individually in E. coli BL21(DE3). The refolded EsxG·EsxH complex was purified by nickel affinity chromatography followed by gel filtration. NMR spectroscopy was then used to solve high resolution solution structure of the protein complex. The minimal shift approach was finally used to analyze the changes in the positions of EsxG·EsxH backbone amide NMR signals resulting from Zn2+ binding.

Results and Conclusion: Here, we report the high resolution solution structure of the M. tuberculosis EsxG·EsxH protein complex, which confirms the expected similarity to the core structure of the EsxA·EsxB complex but reveals striking differences in surface features and properties, including the identification of a potential functional site and a specific Zn2+ binding site. In contrast to EsxA·EsxB, we obtained no evidence for a specific interaction between fluorescently labeled EsxG·EsxH complex and the surface of macrophage/monocyte-like cells. The surface features of both complexes point to roles mediated via interactions with target proteins or complexes. However, striking differences clearly suggest different binding partners, reflecting proposed roles for EsxA·EsxB in pathogen-host cell signaling and for EsxG·EsxH in iron and zinc acquisition by infecting mycobacteria.

Funding:

Class of Presentor: Pharmacy Student
COP Affiliation: Other
THE ROLE OF GENDER IN STUDENTS’ DECISION TO PURSUE PHARMACY AS A MAJOR: A QUALITATIVE STUDY

Meghan Kamath  Diane Ginsburg, UT Austin College of Pharmacy, HOPP

Body of Abstract: Background: Though once male-dominated, the profession of pharmacy has shifted to an increasingly female-dominated field in the United States. There is little research on differences between male and female students’ motivations to pursue pharmacy over other similar majors and career paths.

Objective: This study seeks to explore preliminary reasons for why men and women choose to pursue pharmacy using an in-depth qualitative approach, especially focusing on differences between men and women and why pharmacy was chosen over other similar health profession majors.

Methods: Ten male and ten female Doctor of Pharmacy students at the University of Texas at Austin College of Pharmacy were individually interviewed about why they chose to pursue pharmacy school. Interviews were transcribed and coded to find themes in stated motivations.

Results: Analysis suggests that monetary outcomes, past experience in pharmacy, reduced physical interaction with patients, and reduced stress were important to male versus female participants. Job related autonomy, past experience with a pharmacist of the same gender, and work schedule were important to female versus male participants. Notably, almost all male participants stated they did not believe gender played a role in their decision to pursue pharmacy, whereas less than half of female participants did not think so.

Conclusion: This study suggests male and female students may have different reasons for pursuing pharmacy as a major. Looking at the reasons why women pursue pharmacy by attending a college of pharmacy can help us understand if and how women’s motivation for entering the profession impacts their role in pharmacy. Since predominantly female professions tend to be viewed as lower status and pay than predominantly male professionals, this distinction may become increasingly important for how the profession progresses.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: HOPP
THE EFFECT OF PRENATAL EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS ON NEURAL CELL BIRTH AND DEATH IN THE HYPOTHALAMUS

Melissa Kang, Morgan Hernandez, Andrea Gore. UT Austin College of Pharmacy Department of Pharmacology and Toxicology

Body of Abstract: Human exposure to endocrine disrupting chemicals (EDCs), including polychlorinated biphenyls (PCBs), has detrimental effects on health with clear impacts on endocrine and neurobiological processes from birth to adulthood. Gonadal hormones play a role in brain neurogenesis during critical development periods when fluctuations in estrogen or testosterone can determine whether cells proliferate or undergo apoptosis. Disruptions of these hormones by EDCs can alter brain development and subsequent behavior.

This study is investigating the effect of EDC exposure on neural birth (neurogenesis) and cell death (apoptosis) in the paraventricular nucleus (PVN) of the hypothalamus.

Rat dams were mated, and pregnant rats randomly assigned to treatment groups. Rats were exposed to PCBs by daily intraperitoneal injection from embryonic day (E) 8–E18 with one of 3 treatments: 0.1 ml of vehicle (6% DMSO in sesame oil); 50 µg/kg estradiol benzoate; or 1mg/kg Aroclor 1221, an industrial PCB mixture. To determine the birthdate of neurons, dams received a single intraperitoneal injection of bromodeoxyuridine (BrdU) on E12, E14, or E16. On the day after birth, postnatal day (P)1, we determined birth outcomes and sex ratio. One male and 1 female per litter were euthanized humanely by perfusion at P1, the brain removed, and sectioned on a vibratome. Brain sections through the PVN are being used for immunohistochemistry studies. To identify apoptotic neurons, the TUNEL method will be used to stain nucleosomal DNA fragments that are indicative of apoptotic cells. To determine birthdates of cells, immunohistochemistry of BrdU will be conducted in alternate brain sections. Cells labeled with TUNEL or BrdU will be counted unilaterally using fluorescence microscopy.

To date, we have completed the animal work, sectioned brains, and prepared to run the TUNEL assays and label for BrdU. Based on previously published work, we hypothesize the estradiol benzoate and Aroclor 1221 treatments will advance the timing of neurogenesis and increase apoptosis in the PVN.

Prenatal EDC exposure affects the developing brain, but the specifics of this are unknown. Our study will enable us to determine whether these changes in the PVN are observable as early as P1. If so, this disruption can influence postnatal development, physiology, and behavior.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharm/Tox

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METFORMIN TO IMPROVE THE EFFECTIVENESS OF PNEUMOCOCCAL VACCINES IN OLDER ADULTS

Samantha Le, Annie Liu, Ralph Galega, James Shurko, Grace C. Lee
UT Austin College of Pharmacy, Division of Pharmacotherapy and UT Health San Antonio

Body of Abstract: Background: Streptococcus pneumoniae is a leading cause of community acquired pneumonia and is responsible for 15-40% of all deaths among older adults worldwide. Despite available vaccinations (PPSV23 and PCV13), older adults remain at high risk for infections due to poor vaccine response and age-related immune deterioration. Metformin (MET), a diabetes medication, has the potential to improve immune response through immunoregulatory and anti-aging effects. The aim of this study was to evaluate the impact of MET on pneumococcal vaccine effectiveness in a national cohort of older adults.

Methods: We conducted a retrospective analyses using data from a national health plan. Eligible participants were older adults (> 50 years) with diabetes who received their first pneumococcal vaccine (PPSV23 or PCV13) from Jan 1st, 2013 to Dec 31st, 2015. MET users were defined as patients who filled > 1 prescription for MET within the 90 days prior to the pneumococcal vaccine. Non-users were defined as patients who did not fill a prescription for MET within 12 months of vaccination. Patient demographics, comorbidities, and prior or concomitant medications for diabetes were evaluated. The primary outcome was hospitalization due to pneumococcal sepsis and/or pneumonia 12 months after receipt of the pneumococcal vaccine. A multivariable logistic regression model was used to identify factors associated with hospitalization for a pneumococcal infection. Age, sex, year, and diabetes medications were included as covariates in the model.

Results: A total of 86,051 patients met inclusion criteria; 14,746 were MET users and 71,305 were non-MET users. MET use was significantly associated with reduced risk of hospitalization for pneumococcal infections (aOR= 0.56, 95% CI [0.4 - 0.7]). Patients who received the PPSV23 vaccine had a higher risk of hospitalization due to pneumococcal sepsis or pneumonia compared to those who received PCV13 (OR 3.7 [2.0-6.7]). No differences were found in MET dosing (mean dose=1450mg/d) and outcomes for either vaccine.

Conclusion: MET use was associated with a protective effect for pneumococcal infections and has the potential to improve vaccine effectiveness in older adults.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharmacotherapy

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Abstract 61

SUSCEPTIBILITY TO CEFTOLOZANE/TAZOBACTAM IN CARBAPENEM-RESISTANT PSEUDOMONAS AERUGINOSA

Elijah Martin James Shurko, PharmD, Tiffany Wu, Stephen Tomasek, Andrew Rubio, Grace Lee, PhD, PharmD, BCPS
The University of Texas at Austin, College of Pharmacy, Division of Pharmacotherapy and The University of Texas Health San Antonio

Body of Abstract: Background: Pseudomonas aeruginosa remains an important cause of hospital-acquired infections in the United States. Many P. aeruginosa strains have become multidrug resistant (MDR) through multiple mechanisms, and are often resistant to carbapenems and other beta-lactams. Ceftolozane is a novel cephalosporin with enhanced activity against P. aeruginosa combined with the well-described beta-lactamase inhibitor tazobactam. The purpose of this study was to evaluate the in vitro activity of ceftolozane/tazobactam and relevant comparators against clinical isolates of carbapenem-resistant P. aeruginosa.

Methods: Antimicrobial susceptibilities were determined for 46 meropenem-resistant P. aeruginosa strains from unique patients and minimal inhibitory concentrations (MIC) were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints. Isolates testing non-susceptible to at least one agent in ≥ 3 antimicrobial classes were defined as MDR and isolates testing non-susceptible to at least one agent in ≥ 5 antimicrobial classes were defined as extensively drug resistant (XDR).

Results: Of the 46 meropenem-resistant strains tested, 89.1% were classified as MDR and 39.1% were classified as XDR. Ceftolozane/tazobactam demonstrated 100% in vitro activity versus both MDR and XDR isolates. Strains were sensitive to amikacin and ceftazidime, and susceptibilities were 38.6% for aztreonam, 63% for ceftazidime, 60.9% for gentamicin, 17.4% for levofloxacin, 20.0% for piperacillin/tazobactam, and 69.6% for tobramycin.

Conclusions: Ceftolozane/tazobactam demonstrated in vitro effectiveness against both MDR and XDR carbapenem-resistant P. aeruginosa strains, supporting the potential value of this therapy in treatment of resistant P. aeruginosa infections.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharmacotherapy

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OPERATION NALOXONE: MULTI-INSTITUTIONAL OPIOID OVERDOSE PREVENTION SERVICE LEARNING FOR HEALTH PROFESSIONS STUDENTS

Lubna Mazin Lucas Hill Pharm.D., BCPS, BCACP, Kirk Evoy, PharmD, BCACP, BC-ADM, CTTS, Kenneth Lawson, Ph.D. Affiliation: UT Austin College of Pharmacy, Division of Health Outcomes and Pharmacy Practice

Body of Abstract: In respond to the Opioid Overdose Crisis in the United States, the University of Texas at Austin College of Pharmacy partnered with the Steve Hicks School of Social Work and community partners to combat the crisis together. The objective was to prepare health professions students to train community members to respond effectively to opioid overdoses with naloxone, and to determine the effect of program participation on overdose-related knowledge, self-efficacy, and attitudes regarding harm reduction. Faculty and student directors from The University of Texas at Austin College of Pharmacy led a series of 90-minute train-the-trainer seminars for health professions students (pharmacy, medicine, nursing, and social work) in Austin, San Antonio, and Houston. These seminars provided foundational knowledge regarding opioid overdose epidemiology, risk factors, symptoms, evidence-based response, naloxone formulations, case scenarios, and anticipated questions from community members. Pre- and post-training assessments were embedded within the seminar. Participants were invited to volunteer in a series of community outreach events to provide overdose prevention education to community members. A follow-up assessment was administered electronically approximately three months after the initial seminars. 344 health professions students were trained by Operation Naloxone. These subjects demonstrated significantly improved overdose-related knowledge and self-efficacy, as well as more positive attitudes regarding harm reduction, after training. While these scores declined slightly after three months, they continued to be significantly higher than baseline. Participation in community outreach events did not affect results of the follow-up assessment. A service learning program model may be effective in impacting students’ knowledge, self-efficacy, and attitudes through initial training. Brief community outreach is likely insufficient to further enhance these outcomes, and extensive community engagement should be emphasized when possible.

Funding: n/a

Class of Presenter: Pharmacy Student
COP Affiliation: HOPP
OPERATION NALOXONE: INTERPROFESSIONAL OVERDOSE PREVENTION SERVICE LEARNING

Kimberly Nguyen Lindsey Groff, Khine Tun, Thuy Nguyen, Kirk Evoy, Lucas Hill
UT Austin College of Pharmacy

Body of Abstract: Background: Opioid overdose is the fastest growing cause of death in the United States. Operation Naloxone is an overdose prevention program in which students are trained and subsequently lead trainings related to opioid overdose response, including the proper use of the opioid reversal agent naloxone, and to increase access to naloxone within the community.

Objective: The goals of this project were to: 1) conduct train-the-trainer sessions open to all University of Texas Health San Antonio (UTHSA) students; 2) provide trainings and naloxone supply for vulnerable populations; and 3) assess the training effectiveness.

Methods: UT Austin College of Pharmacy faculty members led two trainings for UTHSA students. Trained students participated in three interprofessional, student-led overdose prevention trainings for drug rehab center residents and staff. Pre- and post-training surveys were administered to student and rehab center training attendees to evaluate the impact on knowledge and attitudes regarding naloxone use and the interprofessional learning experience.

Results: 84 UTHSA students were trained to provide naloxone education. Student-led trainings reached 272 rehab center residents and staff. Results displayed a significant increase (61% vs. 76%, p<0.0001) in mean knowledge, self-efficacy (median 3.5 vs. 5, p<0.0001) and attitude on harm reduction scores (4 vs. 5, p<0.0001). Interprofessional competencies of student participants also significantly increased (median 6 vs. 7, p=0.002).

Conclusion: Through this project, UTHSA students were trained to provide opioid education and subsequently led trainings for vulnerable populations in Bexar County regarding appropriate opioid overdose response, and naloxone was provided to three rehab centers.

Funding: Center for Medical Humanities & Ethics at UT Health San Antonio

Class of Presenter: Pharmacy Student
COP Affiliation: Pharmacotherapy
AGE-RELATED CHANGES IN THE MARMOSET GUT MICROBIOME

Shrina S. Patel, PharmD Candidate1,2 Corinna N. Ross, PhD3; Kelly R. Reveles, PharmD, PhD1,2
1. College of Pharmacy, The University of Texas at Austin
2. Pharmacotherapy Education & Research Center, UT Health San Antonio
3. Texas A&M University San Antonio

Body of Abstract: Introduction: An individual’s health and wellbeing were once thought to be solely due to genes and environment; however, health is likely associated with a broader metagenome phenotype as a result of our microbiome. Variability in human microbiome communities has been associated with infection, obesity, cognitive decline, cancer risk, and frailty. The objective of this study was to compare the gut microbiome diversity and composition between young and old marmosets.

Methods: This was a cross-sectional study of marmosets housed at the Barshop Institute for Longevity and Aging Studies in San Antonio, TX. Stool samples were collected from old (8+ years) and young males (2-5 years) not receiving probiotics, antibiotics, or rapamycin treatment. Samples were sent to Second Genome, Inc. (San Francisco, CA) for sequencing and analysis. Stool 16s rRNA V4 sequences were amplified and sequenced on Illumina MiSeq platform. The sequences were clustered into operational taxonomic units (OTUs) and classified via mothur’s Bayesian classifier referenced against the Greengenes database. Abundance-weighted sample differences were calculated using the Bray-Curtis dissimilarity. The Wilcoxon rank sum test was used to assess variance in relative abundance of taxa between samples. Hierarchical clustering was performed using the Ward2 method.

Results: A total of 10 young and 10 old marmosets were included in the study. Young marmosets had a mean Shannon diversity of 3.46 while old marmosets had a mean Shannon diversity of 3.15 (p=0.0191). At the phylum level, old marmosets had a significantly higher mean abundance of Proteobacteria (0.22 vs. 0.09; p=0.0233) and lower abundance of Firmicutes (0.15 vs. 0.19; p=0.0032) compared to young marmosets. At the family level, old marmosets had a significantly higher abundance of Succinivibrionaceae (0.16 vs. 0.01; p=0.0191) and lower abundance of Porphyromonadaceae (0.07 vs. 0.11; p=0.0494). Beta diversity was significantly associated with age (p=0.019). Hierarchical clustering partially separated samples by age.

Conclusions: Old marmosets had significantly altered microbiome diversity and composition compared to young marmosets. Further studies are needed to test microbiome-targeted therapies to improve healthspan and lifespan.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Other
IMPACT OF THE SUPPLEMENTAL NUTRITION ASSISTANCE PROGRAM ON PHARMACY STUDENTS' DIET AND ATTITUDE TOWARDS FOOD INSECURITY

Huda Razzack Suman Augsteen, Yi Kee Poon, Brenda Astorga, UT Austin College of Pharmacy, Student Society of Health-System Pharmacists and Student National Pharmaceutical Association

Body of Abstract: Background: Food insecurity is a lack of consistent access to enough food for an active, healthy life. It is a complex problem that impacts every community in the United States. An estimated 42 million, including 13 million children, are food insecure. Pharmacists play a key role in providing healthcare to patients whose disease state management is often linked to proper nutrition.

Objective: To simulate a supplemental nutrition assistance program (SNAP) challenge in order to educate pharmacy students on food insecurities and its role in recommending diet plans to patients with limited resources.

Methods: Thirty students from the Student Society of Health-System Pharmacists and Student National Pharmaceutical Association at the University of Texas College of Pharmacy participated in the SNAP challenge. A pre-survey was utilized to gather preliminary information about food insecurity, nutrient consumption, and weekly food spending habits. Over three days of the challenge, participants were instructed to spend no more than $4.40 per day on food. Each participant received meal charts to record food and cost information. At the end of the challenge, a post-survey reassessed their nutrient consumption during the challenge and their understanding of food insecurity.

Conclusion: After completing the SNAP challenge and exploring effects of food insecurity, students were more aware of the impact it has on following physician-recommended diet plans. Participants' understanding of food insecurity increased by 68.6%. In terms of diet, student consumption of carbohydrates increased, meat consumption decreased, protein consumption increased, and fruit and vegetable consumption decreased.

Disclosures: The authors of this presentation have nothing to disclose.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Other
ASSESSING NEW ACC/AHA HIGH BLOOD PRESSURE GUIDELINES AND CREATING A TOOL TO ASSESS OUTCOME OF MEDICATION THERAPY MANAGEMENT SERVICES PROVIDED BY KNOW YOUR MEDICINE (KYM) EVENTS

Judith Rendon Dr. Carolyn Brown, The University of Texas at Austin College of Pharmacy Professor in the Division of Health Outcomes in Pharmacy Practice

Professor Sharon Rush, The University of Texas at Austin College of Pharmacy Clinical Professor in the Division of Health Outcomes in Pharmacy Practice

Body of Abstract: Background: This study is to better understand how the 2017 American College of Cardiology/American Heart Association (ACC/AHA) High Blood Pressure Guideline update affects recommendations made to patients who participate in KYM events.

Objectives: This research aims to compare the number of patients recommended at follow-up pre and post guideline update, determine demographic differences (if any) in the new post-guideline group, and to use these comparisons for the development of longitudinal medication outcome measures in hypertensive patients.

Methods: Secondary data from KYM was used to address the study's objectives. The KYM database consists of health screenings and medication reviews for Texas residents collected via an electronic medication review form. Descriptive and inferential statistics will be used to analyze data and address research objectives.

Results: Based on the more stringent ACC/AHA hypertension guidelines, preliminary analyses of five sites indicate an additional nine patients would have been recommended for physician follow-up. Further analyses will examine if this new group of recommended patients differ from those prior to guideline implementation and inform the development of longitudinal outcome measures.

Conclusions: Preliminary results indicate that more patients will be recommended for physician follow-up and highlight the importance of implementing long-term monitoring for an increasingly larger hypertensive population.

Funding: None

Class of Presentor: Pharmacy Student
COP Affiliation: Honors Student

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**Antimicrobial Susceptibility Profiles and Resistance Markers of Colistin Resistant Carbapenem Resistant Enterobacteriaceae**

**Andrew Rubio** Tiffany Wu, Stephen Tomasek, James Shurko, PharmD, Grace Lee, PharmD, BCPS  
The University of Texas at Austin, College of Pharmacy, Division of Pharmacotherapy and The University of Texas Health San Antonio

**Body of Abstract:** Background: The Centers for Disease Control and Prevention has highlighted Carbapenem-resistant Enterobacteriaceae (CRE) as one of the three highest public health threats. CRE has gained resistance to nearly all antibiotics. These bacteria, already having resistance to carbapenems, have also become an alarming health concern due to their increase in resistance to colistin, an antibiotic often reserved as last resort. In this study, we characterized the resistance profiles of colistin resistant CRE (CR-CRE) strains and colistin susceptible CRE (CS-CRE) strains.

Methods: Carbapenem susceptibility was defined based on an in vitro MIC to meropenem and ertapenem: meropenem MIC ≥ 2 µg/mL or an MIC to ertapenem > 1 µg/mL to be considered non-susceptible. Antimicrobial susceptibilities were determined using minimal inhibitory concentrations (MICs) against 20 antibiotics, and interpreted according to the Clinical and Laboratory Standards Institute breakpoints. Each CR-CRE isolate was matched 1:1 to a CS-CRE isolate by species. The resistance profiles were compared using chi square test. A p-value of < 0.5 was considered statistically significant.

Results: Overall, we evaluated the resistance profiles of 52 CRE (26 colistin-resistant and 26 colistin-susceptible). Of these, 50% were K. pneumoniae, 4% C. amalonaticus, 35% E. cloacae, 5% E. coli, 4% other Enterobacteriaceae sp., and 2% were P. rettgeri. Generally, CS-CRE showed higher susceptibility to all antibiotics tested compared to (CR-CRE): (88% vs 81% for amikacin; p=0.44), (26% vs. 23% for gentamicin; p=0.78), (24% vs 31% for cefepime; p=0.53), (50% vs 8% for meropenem; p<0.01), (31% vs 8% for ciprofloxacin; p=0.03), (35% vs 8% for levofloxacin; p=0.02), (58% vs 8% for tetracycline; p<0.01), and (46% for both CR-CRE and CS-CRE for trimethoprim/sulfamethoxazole).

Conclusions: In conclusion, CS-CRE were susceptible to more antibiotics than CR-CRE, with the exception of cefepime. Amikacin demonstrated the highest susceptibility profile for carbapenem resistant CRE. All other antibiotics tested demonstrated poor activity for both CR-CRE and CS-CRE, showing a greater need for antimicrobial stewardship, strategies for combination therapy, and advancements in antibiotic development for CRE.

**Funding:** n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharmacotherapy

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THE REGULATORY LOOP OF ELONGATION FACTOR 2 KINASE (EEF-2K) CONTRIBUTES TO ITS ACTIVATION BY CA2+-CALMODULIN

Emily Sartain

David H. Giles, Nathan Will, Kwangwoon Lee, Ranajeet Ghose, Kevin N. Dalby

Body of Abstract: Eukaryotic elongation factor-2 kinase (eEF-2K) is a calcium/calmodulin (Ca2+/CaM)-dependent protein kinase that phosphorylates eukaryotic elongation factor 2 (eEF-2) on Thr-56, leading to a reduction in protein synthesis rates. When nutrients are depleted in the cell, eEF-2K plays an essential role in conserving energy by halting protein synthesis. Notably, eEF-2K expression is upregulated in aggressive cancer cells and allows the cells to thrive under nutrient deprivation. The mechanism of eEF-2K activation involves two distinct allosteric steps. First, Ca2+/CaM binds eEF-2K and restructures the active site, rendering the enzyme partially active. This catalyzes phosphoryl-transfer of threonine 348 (Thr-348) on its regulatory loop (R-loop). Autophosphorylation at the Thr-348 site shifts the R-loop away from the active site and allows eEF-2K to be completely active towards eEF-2 when CaM is bound. In addition to Thr-348, the regulatory loop contains phosphorylation sites for a number of upstream kinases known to inhibit eEF-2K activity. However, the exact mechanism whereby these regulatory phosphorylations alter eEF-2K activity is not known.

To investigate how the R-loop drives eEF-2K regulation, we use a minimal construct (termed ΔG6) that lacks 70 residues at the N-terminus and the majority of the R-loop, but retains the critical Thr-348 site. Autophosphorylation of Thr-348 is conserved in ΔG6, and occurs at a rate comparable to that of the WT enzyme. Further, ΔG6 retains its ability to phosphorylate eEF-2 in cells, suggesting the R-loop is not required for eEF-2K to obtain its active conformation. Interestingly, the EC50 of the ΔG6 mutant for CaM is enhanced 10-fold compared to the WT enzyme. This suggests that the regulatory loop plays a role in sensitizing eEF-2K to activation by CaM. We hypothesize that phosphorylation of the R-loop by upstream kinases alters the ability of CaM to activate the enzyme, providing control over eEF-2K activity in cells.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: CBMC
INTERACTING WITH OLDER ADULTS: 
IMPROVING COMFORT LEVEL AND EMPATHY VIA SIMULATION

Sam Shrestha Holli Temple, Karen Rascati
University of Texas at Austin College of Pharmacy
Health Outcomes and Pharmacy Practice

Body of Abstract: Purpose of Study: To determine whether participating in aging simulation activities affected student comfort level and empathy toward interacting with older adults

Background: In Fall 2017, P1 students participated in simulated aging activities during a designated discussion session associated with the Introduction to Patient Care course. Simulated aging activities required students to:
• Button shirts and tie shoes while wearing gloves taped at the joints
• Put popcorn kernels in socks, put on shoes, and walk
• Read prescription information while wearing goggles taped to decrease field of vision
• Participate in a medication counseling session while wearing noise reducing headphones
• Participate in scenarios where beloved friends, family members, hobbies, and possessions are taken away

Methods: Before and after participating in the aging simulation, students responded to survey questions about their comfort level interacting with individuals who have vision or hearing impairment. Students were also asked how hearing impairment affects communication, why it takes longer for elders to complete tasks, and about the sense of loss felt by elders. Other survey questions included how elders are perceived, the number of interactions with those who are hearing or vision impaired, and how students can apply concepts learned in the aging simulation.

Pre/Post Simulation Results: Increased comfort levels related to interacting with individuals who have vision and hearing impairment were statistically significant. A statistically significant increase in understanding an elder’s sense of loss was also noted. No statistically significant differences were found for the other questions.

Conclusions: The aging simulation, specifically the hearing and vision impairment activities and sense of loss scenarios, positively affected student comfort level and empathy toward interacting with older adults. For future offerings, consider using validated instruments to learn about changes in empathy and attitudes before and after participating in the aging simulation. Also consider asking about comfort level when interacting with individuals who have experienced significant loss before and after the simulation.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: HOPP

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REAL-WORLD USE OF CANGRELOR IN A PRIVATE HEALTHCARE SYSTEM

Emily A Siegrist  
Connor Zheng, PharmD Candidate 2018, Lydia Chen, PharmD, BCPS

Body of Abstract: Purpose: Cangrelor is the newest antiplatelet agent approved for prevention of thromboses in patients undergoing percutaneous coronary intervention (PCI). Cangrelor is a unique P2Y12 inhibitor because it is the only agent which can be given intravenously, has a rapid onset and offset, and is reversible. The patient population in which cangrelor should be used has not been well elucidated. This study was conducted to describe the use of cangrelor in a private hospital setting, to discuss potential adverse effects related to cangrelor, and to evaluate anticoagulants and antiplatelets which are used concomitantly.

Methods: The institutional review board approved this retrospective, observational study. Meditech electronic medical record and Vigilanz software were used to identify adult patients who received cangrelor between September 1, 2015 and May 31, 2017. Charts were reviewed and concomitant anticoagulant and antiplatelet agents and bleeding events were recorded.

Results: 157 patients received cangrelor, of which 45.9% (72/157) were diagnosed with ST-elevation myocardial infarction (STEMI), 29.9% (47/157) were diagnosed with non-ST-elevation myocardial infarction (NSTEMI), 3.2% (5/157) were diagnosed with unstable angina (UA), 14.0% (22/157) received elective procedures, and 7.0% (11/157) had other diagnoses. Three patients received extended cangrelor infusions. Ticagrelor was the most commonly used antiplatelet agent, followed by clopidogrel and prasugrel (78.4%, 9.9%, 2%, respectively). Bivalirudin was used in 87.2% (137/157) of patients receiving cangrelor, while argatroban was used in 1.9% (3/157). Five patients experienced re-thrombosis at one week.

Conclusion: In this healthcare system, cangrelor is used primarily in STEMI patients and is commonly co-administered with bivalirudin for anticoagulation and ticagrelor for an antiplatelet load. The usage in elective PCIs was higher than was expected. During this study no institutional guideline was used to direct cangrelor usage. However, an institutional guideline may be useful to support appropriate and cost-effective use based on data from other institutions. More studies are needed to determine the role of cangrelor in clinical settings outside of ACS.

Funding: None

Class of Presentor: Pharmacy Student  
COP Affiliation: Pharmacotherapy

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Abstract 70
PREVALENCE OF HETEROGENOUS VANCOMYCIN-INTERMEDIATE STAPHYLOCOCCUS AUREUS IN A COLLECTION OF CLINICAL METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS ISOLATES

Stephen Tomasek

James Shurko, PharmD, Ralph Galega, PharmD Candidate, Andrew Rubio, PharmD Candidate, Samantha Le, PharmD Candidate, Grace Lee, PharmD, PhD, BCPS

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Body of Abstract: Background: Increased resistance to vancomycin (VAN) has occurred due to its widespread use in the treatment of gram-positive infections. Fully-resistant S. aureus strains have been identified, but vancomycin-intermediate S. aureus (VISA) and heterogeneous VISA (hVISA) strains are more common and are associated with poor outcomes. Because hVISA can be challenging to identify, prevalence is unclear and varies significantly among different studies. Identification of hVISA may help predict poor response to VAN in patients with MRSA infections.

Objective: The objective of this study was to identify the prevalence of VISA and hVISA in a collection of clinical methicillin-resistant S. aureus (MRSA) isolates and to determine if there is a correlation between minimum inhibitory concentration (MIC) and presence of hVISA.

Methods: Clinical MRSA isolates were collected from unique patients in South Texas. Isolates underwent susceptibility testing using VAN Etest strips. Plates were incubated for 24 h at 37°C. Isolates with an MIC ranging from 4-8 µg/mL were classified as VISA, while isolates with an MIC below 4 µg/mL were further screened to identify the presence of hVISA. Screening for hVISA was performed using brain heart infusion agar (BHIA) impregnated with VAN at a concentration of 3 µg/mL. Four 10-µL droplets were plated before incubation at 37°C, and a positive test was defined as growth after 48 h.

Results: A total of 320 MRSA isolates underwent susceptibility testing. The VAN MIC ranged from <0.5 to 2 µg/mL. Of these samples, 239, 74, and 7 had an MIC of ≤1, 1.5, and 2 µg/mL, respectively. None of these samples were classified as VISA. BHIA screening for hVISA was conducted on 174 isolates, and of these, 21 (12.1%) were positive. The proportion of hVISA was 11.6%, 12.5%, and 33% for VAN MICs of 1, 1.5, and 2 µg/mL, respectively. Confirmatory tests to validate the hVISA phenotype are currently underway.

Conclusion: In this collection of MRSA isolates, the overall frequency of hVISA was 12.1% and was highest among isolates with an MIC of 2 µg/mL. A larger sample size and additional confirmatory methods may substantiate this finding.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharmacotherapy
Abstract 72

IMPACT OF A GRAM-NEGATIVE BLOOD CULTURE NUCLEIC ACID RAPID TEST WITH ANTIMICROBIAL STEWARDSHIP INTERVENTIONS AGAINST GRAM-NEGATIVE BACTEREMIA AT A LARGE COMMUNITY HOSPITAL

Khine Tun, PharmD Candidate Jordan Meckel, PharmD Candidate, Gerard Gawrys, PharmD, BCPS, Grace C. Lee, PharmD, PhD, BCPS Pharmacotherapy Division, The University of Texas at Austin College of Pharmacy and Methodist Hospital, San Antonio, TX, USA, 2Methodist Hospital, San Antonio, TX, USA

Body of Abstract: Introduction: The rapid identification of pathogens and resistance determinants is vital for the management of blood stream infections; however, standard microbiological testing typically requires 24-72 hours for results. The Verigene® Gram-Negative Blood Culture nucleic acid test (BC-GN) is a rapid diagnostic test to detect GN organisms and resistance markers from BC, with a turnaround time of 2 hours.

Rationale: There is limited data evaluating the impact of BC-GN on outcomes. The objective of this study was to assess the impact of BC-GN with active antimicrobial stewardship team (AST) on time to antimicrobial optimization and clinical outcomes.

Method: This was a retrospective pre- and post-intervention study conducted at Methodist Hospital San Antonio. Clinical isolates from adult patients with GN bacteremia were included: from July 1, 2012 to July 31, 2014 in pre-intervention group (prior to BC-GN and AST) and from July 1, 2015 to July 31, 2017 in post-intervention group (after BC-GN with AST). The time to antimicrobial optimization was evaluated from time of positive gram stain. Categorical variables were analyzed using x2 test and continuous variables were analyzed using student t test. A p value < 0.05 was considered statically significant. All analyses were performed using SPSS 23.0®.

Results: A total of 123 patients were included. There were no significant differences in baseline characteristics between the two groups. The post-intervention group had a significantly higher proportion of patients with optimal antimicrobial therapy by 24 h than the pre-intervention group (50% vs. 5%; p<0.01). Time to optimal therapy from GS was significantly shorter in the post-intervention group compared to the pre-intervention group for both antimicrobial escalation (17 h vs. 51 h; p=0.02) and de-escalation (38 h vs. 72 h; p<0.01). Among patients with MDRO, a higher proportion of the post-intervention group received optimal carbapenem therapy within 24 h compared to the pre-intervention group (85% vs. 50%; p<0.01). No significant differences in hospital mortality and length of stay were found.

Conclusion: The implementation of Verigene® BC-GN test combined with pharmacists' antimicrobial stewardship interventions substantially decreased the time to antimicrobial optimization in patients with GN bacteremia.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharmacotherapy

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Abstract 73

SUPPRESSION OF BREAST CANCER CELL MIGRATION BY NOVEL INHIBITORS THAT TARGET TRANSIENT RECEPTOR POTENTIAL-MELASTATIN-LIKE 7 (TRPM7) KINASE ACTIVITY

Tamer S. Kaoud, Jihyun Park, Xuemei Xie, So Jung Uhm, Jeong Eun Yum, Clint D.J. Tavares, Nancy D Ebelt, Sabrina Van Ravenstein, Micael Cano, Shreya Mitra, Mohamed F. Radwan, Chandra Bartholomeusz and Kevin N. Dalby

Body of Abstract: Introduction: TRPM7 (transient receptor potential melastatin 7) encodes a calcium permeable non-selective cation channel implicated in cell adhesion and magnesium homoeostasis. The TRPM7 gene encodes for a protein kinase whose activity is linked to the control of actomyosin contractility. TRPM7 mediates adhesion and migration of MDA-MB-231 breast cancer cells and recently has been reported to promote breast tumor cell metastasis. The lack of cell-permeable pharmacological inhibitors of the kinase domain represents a barrier to fully understanding kinase function.

Methods: Herein, we describe the discovery of several compounds that target TRPM7 kinase domain and characterize their mechanism of action in-vitro and in-cells.

Results: The discovered compounds were shown to decrease the binding of Myosin IIB to TRPM7 in HEK293 cells and MDA-MB-231 breast cancer cells transfected with pCMV6-TRPM7. When MDA-MB-231 and BT 549 cells were treated with increasing doses of TRPM7-IN-1, no change in cell viability was seen. Interestingly, TRPM7-IN-1 inhibited migration and invasion in the MDA-MB-231 and BT 549 cells that is reportedly regulated by TRPM7 kinase activity. Finally, magnesium starvation, which promotes TRPM7 kinase activity, induces phosphorylation of eEF2. Treatment of Mg2+-starved HEK293 cells with several of the compounds decreased eEF2 phosphorylation under conditions of magnesium starvation, consistent with the notion that they inhibit TRPM7 kinase activity in cells.

Conclusion: The discovered compounds represent a new group of inhibitors that target the kinase activity of transient receptor potential melastatin 7 (TRPM7) which inhibited breast cancer cell migration.

Funding:

Class of Presentor: Pharmacy Student
COP Affiliation: Other

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THE RESISTOME AND MOLECULAR BASIS OF CLINICAL COLISTIN-RESISTANT KLEBSIELLA PNEUMONIAE

Tiffany Wu Stephen Tomasek, Andrew Rubio, James Shurko, PharmD, Grace Lee, PhD, PharmD, BCPS The University of Texas at Austin, College of Pharmacy, Division of Pharmacotherapy and The University of Texas Health San Antonio

Body of Abstract: Background: The emergence of colistin-resistant Klebsiella pneumoniae (CRKP) is an alarming clinical and public health concern. Colistin is an antibiotic often reserved as a last-resort. Colistin resistance can be either due to chromosomal mutations or to the acquisition of plasmid encoded genes. In this study, we investigated the molecular basis of clinical CRKP strains.

Methods: Whole-genome sequence analysis (WGS) was used to decipher the molecular mechanism of colistin resistance and to identify the resistome harbored by CRKP compared to colistin-susceptible KP (CSKP). Antimicrobial susceptibilities and minimum inhibitory concentrations were determined and interpreted according to the Clinical and Laboratory Standards Institute breakpoints. The resistome was assembled by identifying antimicrobial resistance determinants related to the phenotypically derived antibiogram. Multilocus sequence types (MLST) were classified using WGS data.

Results: Overall, 26 KP were sequenced (13 CRKP and 13 CSKP). These isolates belonged to six different STs (ST37, ST39, ST258, ST307, ST1832, ST2938). The resistome of CRKP isolates was composed of acquired β-lactamases including ESBLs and carbapenemases (blaIMP-27, blaVIM-1, blaKPC-2, blaKPC-3), aminoglycoside (aac, aad, aph, strA), fluoroquinolone (qnr-like, oqx-like), macrolide (mph, mph, ere), phenicol (catA, catB, cmlA, floR), sulphonamide (sul-like), trimethoprim (dfr-like), and tetracycline (tet-like) resistance genes. The resistome of CSKP isolates was similar, but CRKP isolates had more tetracycline, macrolide, and phenicol resistance genes. The resistomes were in accordance with the antibiotic susceptibility testing results. Seven of the eleven CRKP strains had mutations in the mgrB gene. Inactivation of mgrB decreases the affinity of colistin for lipopolysaccharide (LPS). Noteworthy, none of the strains harbored the mcr-1 gene associated with colistin resistance.

Conclusions: Overall, CRKP are resistant to more antibiotic classes than CSKP. The main molecular mechanism for colistin resistance in K. pneumoniae is via the LPS biosynthesis pathways. Additional research is needed to determine other mechanisms for colistin resistance.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Pharmacotherapy
EVALUATION OF A PILOT HOSPITAL SIMULATION ON THIRD-YEAR PHARMACY
STUDENT CLINICAL AND INTERPROFESSIONAL DEVELOPMENT

Stephanie Yin, Molly F. Curran, PharmD, BCPS; Veronica S. Young, PharmD, MPH

Body of Abstract: Purpose: Student opportunities for interprofessional collaboration in an inpatient setting outside of APPE rotations are limited. Thus, a pilot project to simulate patient care in an acute care ward was conducted with nursing and social work students. The pilot was designed to provide third-year students (P3s) a chance for pharmacotherapy knowledge application, experience internal medicine collaborative interprofessional patient care, and evaluate qualitative learning from the simulation experience.

Methods: The pilot took place at the Simulation and Skills Center at The University of Texas School of Nursing during a graded patient care simulation for nursing students. Faculty and students from pharmacy and social work were invited to participate to mirror real-world practice. In Spring 2017, twelve P3 students participated in the pilot as inpatient clinical pharmacists mentored by three P4 students. A same-day debriefing led by a clinical pharmacy faculty member was held with the pharmacy students, as well as a large group debrief led by nursing for all professions. In the following week, three focus groups were conducted with pharmacy students and the collected qualitative data were evaluated to identify education themes and describe the usefulness of the simulation.

Results: A qualitative analysis of focus group data identified five key themes from the simulation experience. The analysis highlighted the utility of early exposure to interprofessional collaborative practice beyond the traditional classroom setting. This exposure helped students form a deeper appreciation of the roles and responsibilities of other professions in the delivery of patient care.

Conclusion: A hospital simulation for third year pharmacy students modeled after an internal medicine APPE rotation is shown to successfully provide students the opportunity to demonstrate pharmacotherapy knowledge, practice clinical skills, and experience interprofessional collaboration at the bedside. All pharmacy student participants recognized the value of the simulation prior to APPE rotations, and recommended that the experience be integrated into curriculum. Barriers to full implementation include the density of the existing curriculum, limited financial resources, faculty availability, and scheduling conflict.

Funding: n/a

Class of Presentor: Pharmacy Student
COP Affiliation: Other

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TRPM7 KINASE DOMAIN IS INVOLVED IN BREAST TUMOR CELL METASTASIS.

Jeong Eun Yum Tamer S. Kaoud1, Xuemei Xie2, Regina A. Mangieri1, Jeong Eun Yum1, So Jung Uhm1, Jihyun Park2, Clint D.J. Tavares3, Nancy D Ebelt1, Sabrina Van Ravenstein1, Micael Cano1, Shreya Mitra2, Mohamed F. Radwan4, Richard A. Morrisett1, Chandra Bartholomeusz2 and Kevin N. Dalby1

1College of Pharmacy, The University of Texas at Austin, Austin, TX, USA; 2MD Anderson Cancer Center, Houston, TX, USA. 3Department of Cancer Biology, Dana-Farber Cancer Institute, and Department of Cell Biology, Harvard Medical School, Boston, Massachusetts, USA. ; 4Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia.

Body of Abstract: Introduction: TRPM7 (transient receptor potential melastatin 7) is a non-selective cation channel fused to protein kinase domain at the C-terminal whose activity is linked to the control of actomyosin contractility. TRPM7 mediates adhesion and migration of breast cancer cells and promotes breast tumor metastasis. The lack of cell-permeable inhibitors of the kinase domain represents a barrier to understand the kinase function.

Methods: Herein, we developed MDA-MB-231 breast cancer cell lines in which TRPM7 is knocked out by CRISPR/Cas9 (KO), and in which various forms of TRPM7 were stably re-expressed. These were wild type TRPM7 (WT), a kinase-inactive mutant of TRPM7 (KD), and TRPM7 containing a truncated kinase domain (KT). By using them, we are investigated the involvement of TRPM7 kinase domain in breast tumor cell metastasis.

Results: TRPM7 KO significantly inhibited MDA-MB-231 cells migration. Only expression of the wild type TRPM7 (WT) rescued the migration phenotype, supporting a role for the kinase domain and not the channel in the regulation of cell migration. When MDA-MB-231 cells were treated with increasing doses of TRPM7 kinase inhibitor (TRPM7-IN-1), TRPM7 phosphorylation at Ser-1569 and its downstream Myosin IIa phosphorylation at Ser1943 were abrogated at a concentration of 5 µM. MDA-MB-231 cells stably expressing a kinase-inactive mutant of TRPM7 (KD) exhibited suppression of Myosin IIa phosphorylation if compared to cells expressing wild type TRPM7 (WT). Electrophysiological assessment of the TRPM7 channel revealed that either treatment of MD-MB-231 cells with TRPM7 kinase inhibitor or using MDA-MB-231 cells stably expressing a kinase-inactive mutant of TRPM7 (KD) did not affect the channel function, supporting the notion that the inhibitor affects the migration exclusively through the inhibition of the TRPM7 kinase domain rather than the channel. Finally, the bioluminescent signals (to assess lung metastasis) were significantly lower in KD-1-treated mice (25 and 50 mg/kg/day) than in mice treated with vehicle control (P ≤ 0.05, 2-sided t-test.).

Conclusion: Inhibition of TRPM7 kinase activity may reduce or block breast tumor progression and/or metastasis.

Funding: CPRIT & NIH

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EVALUATION OF WEIGHT-STRATIFIED ADENOSINE DOSING FOR PATIENTS WITH SUPRAVENTRICULAR TACHYCARDIA

Sharmin Amjad, Bethany A. Kalich, Ellen Robinson, Amanda Fowler, and Darrel W. Hughes. Department of Pharmacy, University Hospital, University of Texas Health San Antonio, University of Texas Austin College of Pharmacy; University of the Incarnate Word Feik School of Pharmacy, San Antonio, Texas

Body of Abstract: Background: Supraventricular tachycardia (SVT) is a frequent Emergency Department (ED) presentation. Patients with symptomatic SVT require rapid evaluation and administration of appropriate therapy, such as adenosine, to restore normal sinus rhythm (NSR). Little exists in the way of dosing recommendations in patients who are obese or when guideline-recommended doses of intravenous adenosine (6mg, followed by 12mg) fail to control or terminate SVT, of which the former may affect the later.

Objective: Evaluate weight-stratified dosing of adenosine.

Methods: This single center, retrospective chart review was approved by the Institutional Review Board at University Health System and included all adult patients admitted to the ED or Intensive Care Units who received adenosine for management of SVT. Exclusion criteria included: age less than 18 years and those who received adenosine for the purposes of diagnosing tachyarrhythmia. Each individual dose of adenosine was collected and normalized to patient actual body weight. Adenosine doses ≥ 0.1 mg/kg were compared to doses < 0.1 mg/kg for the primary endpoint of termination of SVT. Secondary objectives were to compare number of doses to successful attempt and adverse effects of higher adenosine dosing. Adverse events were defined as the occurrences of either of the following post administration of highest dose of adenosine: bradycardia defined by heart rate < 60 bpm or asystole as seen on EKG.

Results: Forty eight patients were evaluated with a mean age of 58.8 + 16.0 years. The majority of patients (62.5%) were female with a median weight of 75kg (range 66- 91kg). Conversion to NSR occurred in 9/11 (81.8%) vs 19/37 (48.7%) for those who received a dose > 0.1mg/kg vs controls (p=0.08). Post-hoc statistical power of the primary outcome was 49.2% for our sample. For secondary outcomes, 11 (23.9%) patients achieved NSR with the 1 dose while 35 (76.1%) patients required additional doses. No adverse effects were seen with higher doses of adenosine.

Conclusion: There was no significant difference in successful conversion of SVT to NSR based on weight stratified dosing of adenosine, though conversion to NSR was more likely upon repeated dosing.

Funding: n/a

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COP Affiliation: Resident

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STANDARD VS ALTERNATIVE THERAPY FOR STENOTROPHOMONAS MALTOPHILIA INFECTIONS: FOCUS ON TRIMETHOPRIM-SULFAMETHOXAZOLE, MINOCYCLINE, AND MOXIFLOXACIN MONOTHERAPY

Jasmin K. Badwal Elizabeth O. Hand, Kristi A. Traugott
University Health System, University of Texas Health San Antonio, San Antonio, TX
University of Texas at Austin College of Pharmacy, Austin, TX

Body of Abstract: Purpose: To compare the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX), moxifloxacin, or minocycline for treatment of S. maltophilia infections.

Methods: This was a single-center, retrospective chart review from January 2006 – September 2017. Study subjects were selected by cross-referencing billing and culture data. Patients ≥ 18 years of age were included if they had isolated S. maltophilia in at least one culture and were treated with one of the three agents for at least 5 days. Patients were excluded due to pregnancy, incarceration, cystic fibrosis, concurrent antimicrobials with activity against S. maltophilia, or having prior case of treated S. maltophilia infection. Complete success was defined as meeting all three of the following: 1) resolution of signs/symptoms, 2) no repeat isolation within 30 days of discontinuation, and 3) no switch or addition of alternative antibiotics that cover S. maltophilia. Partial success was defined as meeting at least two out of the three criteria. Secondary outcomes included mortality, length of hospital stay (LOS), adverse effects, and resistance development.

Results: A total of 109 patients were included in this study: 37 for minocycline, 40 for moxifloxacin, and 32 for TMP-SMX. Complete clinical success was seen in 47/109 (43%) patients. No statistically significant difference in achievement of complete clinical success was identified: minocycline 17/37 (45.9%) vs moxifloxacin 16/40 (40%) vs TMP-SMX 14/32 (43.7%), p = 0.8674. When including patients that achieved partial clinical success, there was still no significant difference between groups: minocycline 35/37 (94.6%) vs moxifloxacin 34/40 (85%) vs TMP-SMX 29/32 (90.6%), with p = 0.3724. Use of moxifloxacin was associated with significantly longer overall length of stay (p = 0.0340) as well as in the intensive care unit (p = 0.0114). Development of moxifloxacin resistance within 30 days post-treatment was also more common (p = 0.0258). There was no difference in mortality or duration of treatment.

Conclusion: Achievement of clinical success was found to be similar between all three groups. However, moxifloxacin was associated with longer LOS and increased resistance development. Overall applicability may be limited due to the low number of patients included.

Funding: n/a

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IMPACT OF MATRIX-ASSISTED LASER DESORPTION/IONIZATION TIME-OF-FLIGHT MASS SPECTROMETRY (MALDI-TOF MS) ON MANAGEMENT OF PATIENTS WITH GRAM POSITIVE BLOOD CULTURES IN A MULTICENTER HEALTHCARE SYSTEM

Amy Carr  Dell Seton Medical Center at The University of Texas | Department of Pharmacy

Body of Abstract: Introduction: Early appropriate therapy for bloodstream infections decreases morbidity, mortality, and exposure to unnecessary antibiotic therapy. Rapid diagnostic testing of blood specimens in combination with antimicrobial stewardship program support is a recommended tool for reducing time to de-escalation of empiric antibiotics and discontinuation of unnecessary therapy. This study aims to evaluate the impact of Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) for gram-positive organism identification (ID) for blood cultures across a healthcare system comprised of pediatric, adult academic, and adult community hospitals utilizing a central microbiology lab with unique antimicrobial stewardship resources at each site.

Methods: This multicenter retrospective study compared patients with a positive blood culture for a gram-positive organism identified via MALDI-TOF MS to a historical cohort identified by conventional methods. Primary outcome was time to optimal therapy (TTOT). Secondary outcomes included time to effective therapy, duration of therapy, time to microbiologic clearance, hospital length of stay (LOS), ICU LOS, recurrence, readmission, in-hospital mortality, and all-cause mortality.

Results: This study included 129 cultures (12% from pediatric patients) in the conventional period and 129 cultures (19% from pediatric patients) in the MALDI-TOF MS group. Of the total 258 blood cultures included in this study, 147 (57%) represented true bloodstream infection and 111 (43%) were deemed to be contamination. Median time to organism ID was reduced from 60.0 hours with conventional methods to 45.4 hours with MALDI-TOF MS (p<0.001). There was no difference in median time to susceptibility results between the two groups (68.1 hours vs. 66.1 hrs, p=0.239). The primary outcome of median TTOT was not significantly reduced by MALDI-TOF MS (70.7 hours vs. 65.9 hours, p=0.407). There were no significant differences with regard to any of the secondary outcomes.

Conclusion: Utilization of MALDI-TOF MS for organism ID in the absence of antimicrobial stewardship intervention may not reduce time to optimal therapy in patients with gram-positive blood cultures.

Funding: n/a

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Abstract 80

DURATION OF THERAPY OF ANTIBIOTICS FOR STAPHYLOCOCCUS AUREUS BACTEREMIA IN ONCOLOGY PATIENTS

Kori E. Daniels Jon D. Herrington, Elmor D. Pineda
Affiliation: UT Austin College of Pharmacy, Scott & White Medical Center - Temple, Texas

Body of Abstract: Purpose: Staphylococcus aureus bacteremia has been reported to have a mortality rate of 20 - 40%. The IDSA guidelines for the treatment of methicillin-resistant S. aureus recommend treating patients for a minimum of 14 days. However, there are no guidance for the duration of therapy in the oncology population. Due to the lack of information available, the potential for inappropriate or excessive treatment durations could occur. This study’s purpose is to characterize and evaluate the oncology patient outcomes and the duration of antibiotic therapy for S. aureus bacteremia.

Methods: This IRB approved study is a retrospective review from 10/2007-10/2017. Inclusion criteria are at least 18 years of age, at least one positive blood culture of S. aureus, at least 75% of total antibiotic therapy with an appropriate antibiotic, and malignant diagnosis. Exclusion criteria are polymicrobial blood cultures, basal cell or squamous cell carcinoma as only malignancy. The primary endpoint is duration of antibiotic therapy. Secondary endpoints include the composite outcome of death and treatment failure. Exploratory endpoints will be performed as sub-group analyses on any factor that might have influenced duration of therapy and/or treatment failure/death (i.e. Infectious Disease consult, type of malignancy, resistant organism, low serum albumin, shock, and ANC). For statistics, characteristics of the sample are summarized using descriptive statistics. Means and standard deviations (or medians and ranges, if appropriate) are reported for continuous variables. Frequencies and percentages are reported for categorical variables.

Results: The preliminary data include 17 patients with bacteremia. 2 patients were treated with antibiotics for 1-14 days. 5 patients were treated with antibiotics for 15-28 days. 10 patients were treated with antibiotics for longer than 28 days. 1 patient in each group experienced a reinfection. 1 patient died.

Conclusion: Longer durations of antibiotics do not affect treatment failure.

Funding: n/a

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Abstract 81

ADMISSION RATES IN HEART FAILURE PATIENTS BEFORE AND AFTER ENROLLMENT INTO MULTIDISCIPLINARY, TRANSLATIONAL CLINIC

Paige Davies, PharmD Neil Pan, PharmD, BCPS; Eimeira Padilla-Tolentino, PharmD,PhD; Emily Ong, PharmD, BCACP; Holli Sadler, MD

Body of Abstract: Background: High rates of 30-day hospital readmissions incur penalties by the Centers for Medicare and Medicaid Services (CMS). Across the county, the 30-day admission rate of heart failure patients exceeds the rates of other conditions, such as myocardial infarction and pneumonia. Additionally, the national average heart failure admission rate has a larger standard deviation, indicating a variation in the quality of care delivered, and a potential for improvement. A variety of outpatient clinic models have been reported in the literature with the aim of reducing admissions among heart failure patients.

Objective: To evaluate the impact of a multidisciplinary, transitional clinic on admission rates in federally funded, locally funded, and unfunded heart failure patients.

Methods: This self-controlled, retrospective study included heart failure patients enrolled into a multidisciplinary, transitional clinic. A sample size of 538 patients was required to detect a 3% decrease in admission rates from an institutional baseline of 27%. Patients were referred to this service during a hospital admission, and were eligible if at least 18 years of age, and had funding through 1 of 3 sources: CMS, a local program for low income patients, or were unfunded. Patients were excluded if heart failure was not listed as an ongoing problem during a separate admission within the year prior to enrollment. All-cause and heart failure related emergency department or hospital admissions during the 30 and 90 days immediately before and after enrollment were compared.

Results: A total of 149 patients were included in this study. The primary outcome, 30-day, all-cause admissions, was not significantly different before and after enrollment, 27.5% and 34.3% respectively (p= 0.26). Similarly, all-cause admissions 90 days after discharge, was unchanged, 45.6% (p= 1.00) before and after enrollment. The rate of heart failure related admissions in the 30 and 90 day periods slightly decreased after enrollment, from 26.4% to 23.3% (p= 0.70) and from 29.0% to 20.0% (p= 0.28) respectively, but were not significant.

Conclusions: Enrollment into a multidisciplinary, transitional clinic may not affect 30 or 90-day, all-cause admission rates. Its impact on heart failure-related admissions is also unclear and requires a larger study for further assessment.

Funding: n/a

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APPROPRIATE PRESCRIBING OF SULFAMETHOXAZOLE/TRIMETHOPRIM IN GERIATRIC PATIENTS

Elina Delgado, PharmD, MAA  Rebecca Rottman-Sagebiel, PharmD, BCPS, BCPG; Kristin Madden, PharmD, BCPS, BCPG
South Texas Veterans Health Care System, Department of Pharmacy Services

Body of Abstract:  Background: Sulfamethoxazole/Trimethoprim (SMZ/TMP) is an antibiotic frequently prescribed for respiratory, skin and soft tissue (SSTI), and urinary tract infections (UTI) due to ease of dosing and broad bacterial coverage. Although adverse renal effects have been reported, it remains widely prescribed in older adults. Most decreases in renal function are transient with resolution following discontinuation. Kidney injury may persist in a small number of patients. Studies have also shown an increase in hospitalizations when SMZ/TMP is prescribed to patients on ACEi/ARBs and beta-blockers.

Methods: We conducted a quality improvement project to assess the appropriateness of use of SMZ/TMP for older adults at the South Texas Veterans Health Care System. Inpatient and outpatient records from February 2017-January 2018 were pulled. Inclusion criteria were age ≥65 and ≥ 3 days of therapy. Exclusion criteria included initiation prior to 2/2017, prescriptions from non-VA providers, and duplicate orders. To control for confounders, variables such as pertinent concomitant medications, pre-existing health conditions, basic metabolic panel (BMP) and antibiotic indication were collected.

Results: A total of 157 outpatient and 49 inpatient prescriptions for SMZ/TMP were identified, and 63 were excluded. Of the 143 records included, 37 were initiated or completed while inpatient and 106 were outpatient orders. Mean age was 72 years, 94% male, and 66% white/17% Hispanic. The top indications for SMZ/TMP were SSTI (36%), UTI (32%) and prophylaxis (17%). About half of the patients had follow-up BMPs collected within 30 days of SMZ/TMP initiation. Renal function was not affected in 62% of patients. Four patients had a significant increase in SCr (≥ 0.5). Renal function returned to baseline for three patients and for one patient renal function was unknown. No hospitalizations were related to use of SMZ/TMP.

Conclusion: Although SMZ/TMP was found to increase SCr in a small number of the patients reviewed with follow-up labs available, persistent kidney injury did not affect the patient cohort. This was despite the presence of concomitant chronic diseases and medications known to affect kidney function. Based off the initial results of the study, a larger sample is needed to determine true effects.

Funding: n/a

Class of Presentor: Resident
COP Affiliation: Resident
EVALUATING THE IMPACT OF OPIOIDS ON LENGTH OF STAY IN PATIENTS WITH CLOSTRIDIUM DIFFICILE INFECTIONS

Monica Do Jon Herrington, Esther Yi, Jerry Smith, Scott & White Medical Center - Temple, Temple, TX.

Body of Abstract: Purpose: The 2010 Infectious Diseases Society of America (IDSA) and the 2017 American College of Gastroenterology guidelines both recommend the avoidance of antimotility agents in patients with Clostridium difficile infections (CDIs) to prevent complications, but these recommendations are based on poor/low quality evidence. Given the limited evidence available since 2010, the 2018 IDSA guideline no longer contains formal recommendations regarding antimotility use. Opioids have a class effect of decreasing peristalsis. Therefore, the opioid population can be used to examine the possible link between antimotility use and worse outcomes.

Methods: This IRB approved retrospective study evaluated patients over a three-year period. Using data retrospectively collected from the institution’s electronic records, we identified patients with a first time diagnosis of CDI diagnosed within seventy-two-hours of admission. The two groups compared included patients in the no opioid group (NOG), which included patients taking an average of less than or equal to 10 milligrams of oral morphine equivalents (OMEs) per day, and patients in the opioid group (OG), which included patients taking an average of more than 10 milligrams of OMEs per day. The primary endpoint was difference in length of stay (LOS). Secondary endpoints included CDI severity based on the 2010 IDSA classification, recurrence within ninety days, and all-cause mortality within thirty days of diagnosis.

Results: A total of 112 patients were included in this study with 79 patients in the NOG and 45 in the OG. 66% of the study population consisted of females, and the median Charlson Comorbidity Index among both groups was 3. The average ages were 73 and 59 in the NOG and OG respectively. Average LOS was 5.6 in the NOG and 5.58 in the OG, which was found to be not statistically significant. The incidence of severe CDI, complicated CDI and recurrence did not significantly differ between the two groups.

Conclusion: Based on this small retrospective analysis, it appears opioid use may not increase LOS or influence CDI severity. Future prospective studies are needed to confirm this finding.

Funding: n/a

Class of Presentor: Resident
COP Affiliation: Resident
RETROSPECTIVE ANALYSIS OF ASPIRIN VERSUS NON-ASPIRIN THERAPY FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS WHO HAVE UNDERGONE A TOTAL HIP OR KNEE ARTHROPLASTY

Nicole Dominguez, PharmD, Annie Hong, PharmD, BCPS, Brette McDonald, PharmD, Jerry D. Smith, PharmD, BCPS, Sebastian Perez, PharmD, BCPS.

Affiliation: UT Austin College of Pharmacy, Scott & White Medical Center, Temple, TX.

Body of Abstract: Purpose: Over 700,000 individuals receive a total hip arthroplasty (THA) or total knee arthroplasty (TKA) in the United States each year. A major complication associated with THAs and TKAs is venous thromboembolism (VTE). The risk of post-surgical VTE can be mitigated with the use of chemoprophylactic agents; however, there is currently no consensus on what specific agent should be used. The primary objective of this study is to compare aspirin versus non-aspirin therapy for VTE prevention in patients who have undergone a recent THA or TKA.

Methods: This retrospective study provided information on the difference between aspirin and non-aspirin therapy for VTE prevention after orthopedic surgery. Patients included were those diagnosed with a VTE within 6 weeks of having a THA or TKA and were prescribed either aspirin or non-aspirin therapy prior to the event. Secondary analyses will be conducted to identify significant risk factors present and the dose and frequency of aspirin used in patients that had a VTE. Data collected included age, sex, weight, co-morbidities, type of surgery, location of VTE, time between surgery and VTE, and description of the pharmaceutical regimen used for chemoprophylaxis.

Results: Data was collected for surgeries that occurred from February 2014 through October 2017. Sixty percent of those included were female with an average age of 71.6. The majority of those included in this study were prescribed aspirin and the remaining patients were prescribed an anticoagulant (i.e. heparin, warfarin). A total of 20 VTEs were included for analyses. Of those, 10 were classified as a deep vein thrombosis (DVT), 8 were found to be pulmonary embolisms, (PEs), and 2 were a combination of both a DVT and PE.

Conclusions: The immediate goal of this project is to use this data to guide prescribing practices in patients undergoing major orthopedic surgery. However, the small sample size is a significant limitation when interpreting the results of the study.

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EFFECT OF DAILY LOW-DOSE VITAMIN K SUPPLEMENTATION ON INTERNATIONAL NORMALIZED RATIO (INR) STABILITY IN PATIENTS TAKING WARFARIN

Hannah Ehrenfeld, Delaney Ivy, Megan Roberts, Christy Evans, Aimee Nguyen, Linda Chen, Brianne Sorunke
Scott & White Medical Center - Temple, Temple, TX

Body of Abstract: Introduction: Despite advent of direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs) are still widely used in prevention of venous and arterial thromboembolism. Several drawbacks exist with VKAs, including: a narrow therapeutic index, large patient variability, frequent monitoring, and many drug interactions. Despite monitoring with VKAs, INR is within a specified therapeutic range ~60% of time. Consequences of INR outside therapeutic range include risk of bleeding/clotting. Improving INR stability should, in theory, reduce adverse effects seen with under- and over-coagulation. A current theory exists stating patients with low vitamin K stores have greater degrees of INR fluctuation with altered vitamin K intake. The theory postulates low-dose vitamin K supplementation establishes a baseline pool, so changes in intake have reduced effect on INR. To date, only some studies evaluate the use of daily vitamin K supplementation on increased time in therapeutic range (TTR). Further complicating the picture of vitamin K supplementation, the studies had conflicting evidence to support its use. Further, the 2012 CHEST guidelines do not recommend vitamin K supplementation in patients on a VKA (Grade 2C).

Methods: This retrospective review included patients on warfarin, with or without daily vitamin K supplementation at Scott and White Medical Center, > 18 years, need for chronic anticoagulation, and patients on warfarin or warfarin plus vitamin K supplement for > 6 months. The primary endpoint is the difference in TTR between the supplemented and un-supplemented groups. Secondary endpoints are the incidence of major bleeding or thrombotic events.

Results: N=50 were included in the warfarin alone group, and N=48 were included in the vitamin K supplemented group. In regards to the primary outcome, TTR was 75.3% in the warfarin alone group and 69.3% in the low-dose vitamin K supplementation group over a 6 month time frame (p=0.068). Among all 98 patients, 1 experienced a bleed requiring hospitalization during the 6-month time frame observed while none experienced thrombotic events.

Conclusion: Based on the results, there is no significant difference in TTR between the un-supplemented and supplemented groups, but several limitations impact the ability to interpret the data.

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Class of Presentor: Resident
COP Affiliation: Resident
**IMPACT OF THE IMPLEMENTATION OF A RAPID MENINGITIS/ENCEPHALITIS MULTIPLEX POLYMERASE CHAIN REACTION PANEL ON CLINICAL OUTCOMES: MULTICENTER, RETROSPECTIVE COHORT OF ADULT AND PEDIATRIC PATIENTS**

**Martha Evans, PharmD, Seton Healthcare Family** Kathryn Merkel, PharmD, BCPS (AQ-ID), Seton Healthcare Family; Dusten Rose, PharmD, BCPS (AQ-ID), AAHIVP, Seton Healthcare Family

**Body of Abstract:** Purpose: Meningoencephalitis has a high mortality rate. Rapid identification of the underlying etiology is essential to optimize clinical and stewardship outcomes. Until recently, the standard for diagnosis of meningoencephalitis included cerebrospinal fluid (CSF) culture and viral polymerase chain reaction (PCR). In 2015, the FilmArray® BioFire® Meningitis/Encephalitis (ME) panel, a multiplex PCR panel for the detection of central nervous system pathogens, was approved. The ME panel poses advantages over CSF culture and viral PCR in that it simultaneously detects a broad array of 14 pathogens and the results are available in approximately one hour. The objective of this study was to determine the impact on clinical outcomes of the newly adopted ME panel as compared to previously utilized CSF studies within a large, multicenter health system.

Methods: This is a multicenter, retrospective cohort study of adult and pediatric patients who received at least one dose of intravenous (IV) acyclovir for presumed meningoencephalitis, with study patients divided into pre-ME panel and post-ME panel cohorts. The primary endpoint is duration of IV acyclovir before and after implementation of the ME panel. Secondary endpoints include duration of antibacterials, in-hospital mortality, intensive care unit (ICU) length of stay (LOS), hospital LOS, rates of acute kidney injury (AKI), and test-turnaround time.

Results: A total of 208 patients were included in the study. Of the patients included, 87 (41.8%) were pediatric patients and 121 (58.2%) were adults, with a median pediatric age of 22.1 days and a median adult age of 51.1 years. The duration of IV acyclovir decreased after implementation of the ME panel (41.6 versus 30.8 hours; \( p < 0.01 \)). The test-turnaround time was reduced with the implementation of the ME panel (37.3 versus 6.2 hours; \( p < 0.01 \)). There was no difference in the duration of empiric meningoencephalitis antibacterials between the two cohorts. There were no significant differences in in-hospital mortality, hospital LOS, ICU LOS, or rates of AKI between the two groups.

Conclusion: The ME panel significantly reduced the duration of IV acyclovir and test-turnaround time. These results could have cost and safety implications when applied to a larger patient population.

**Funding:** n/a

Class of Presentor: Resident
COP Affiliation: Resident

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OUTCOMES FROM A PHARMACIST MANAGED METABOLIC MONITORING CLINIC FOR PATIENTS PRESCRIBED SECOND GENERATION ANTIPSYCHOTICS AT A VETERANS AFFAIRS HEALTH CARE SYSTEM

Lindsey M. Garner, Pharm.D., MBA, BCPS Ilona Shishko, Pharm.D., BCPP; Troy A. Moore, Pharm. D., M.S.Pharm., BCPP
Affiliation: UT San Antonio College of Pharmacy; South Texas Veteran Health Care System

Body of Abstract: Background: In 2003, the FDA issued a warning for second generation antipsychotics (SGA) regarding an increased risk for diabetes and hyperglycemia. Soon after, in 2004, the American Diabetes Association in collaboration with the American Psychiatric Association published a consensus on antipsychotic drugs and obesity and diabetes (ADA Consensus), which provided a recommended monitoring protocol for patients receiving SGAs. Since these recommendations were made available, several studies have looked at a variety of outcomes regarding monitoring patients taking SGAs, the results of which have called attention to the fact that metabolic monitoring remains subpar. To improve the quality of care provided to veterans and clarify roles for both primary care and mental health providers, the South Texas Veterans Health Care System (STVHCS) piloted a PGY-2 psychiatric pharmacy resident run metabolic monitoring clinic in 2015.

Objectives: To evaluate the metabolic monitoring clinic as a quality improvement measure for veterans on SGAs with the goal of further expanding the clinic.

Methods: Patients scheduled into the PharmD Metabolic Monitoring clinic between 9/1/2015 and 6/30/2016 will be reviewed using the Computerized Patient Record System (CPRS) for the following information: age, gender, smoking status, BMI, weight, select medical diagnoses, and antipsychotic medication. The following information will be collected from notes related to encounters in the PharmD Metabolic Monitoring clinic: indication for SGA medication, metabolic monitoring adherence, metabolic side effect identified and addressed, non-metabolic side effects identified and addressed, medication discontinuation, proportion of missed appointments as a marker of non-adherence to care, and number of encounters.

Outcomes: Primary outcomes are the percentage of patients meeting APA guideline directed metabolic monitoring parameters compared to pre-clinic standard of care, and number of patient encounters. Secondary outcomes include number of patients who developed metabolic side effects, actions taken to address these, causes of suboptimal monitoring, and adherence to appointments.

Results: Results will be presented during the poster session, including how pharmacist interventions differed from standard of care.

Funding: n/a

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**Abstract 88**

**COMPREHENSIVE SMOKING CESSATION THERAPY FROM THE CLINICAL PHARMACIST SPECIALIST SMOKING CESSATION CLINIC VERSUS SMOKING CESSATION PHARMACOTHERAPY ALONE FROM OTHER PRIMARY CARE PROVIDERS AT THE SOUTH TEXAS VETERANS HEALTH CARE SYSTEM**

**Sarah Hallowell** South Texas Veterans Health Care System

**Body of Abstract:** Background & Purpose: Cigarette smoking remains the leading cause of preventable death and disease in the United States, and the prevalence of smoking among Veterans has been reported as higher than in the civilian population. Effective smoking cessation interventions for veterans are therefore critically needed. The primary outcome of this program evaluation is to compare the success of quit attempts 6 months after receiving medication management by Clinical Pharmacy Specialist (CPS) versus management by primary care providers (PCPs). We hypothesize that patients in the CPS group will have greater quit attempt success than those in the PCP group.

Methods: The present investigation consisted of a retrospective chart review using the Veterans Affairs Computerized Patient Record System (CPRS). Adult veterans enrolled in the CPS smoking cessation clinic from July 2014 until the present who received a prescription for nicotine replacement therapy (NRT), including nicotine patches, nicotine lozenges, or nicotine gum, or those who received NRT and bupropion issued on the same day were included, along with a matched number of patients from PCPs. Secondary outcomes include number of follow-up contacts where smoking was addressed after prescription issuance, time to successful quit attempt if achieved, relapse rates, and comparison of amount of information available in CPS and PCP groups. If 6-month quit status is not available in the chart, veterans will be contacted by phone to determine their quit status.

Results: Results will be presented during the poster session, including baseline characteristics, the primary outcome of quit attempt success six months after prescription issuance measured by rates of self-reported abstinence, and the aforementioned secondary outcomes.

Conclusion: This retrospective program evaluation seeks to compare the success of smoking cessation attempts by patients receiving NRT with or without bupropion in the CPS smoking cessation clinic at the STVHCS with success of patients managed by PCPs. If increased quit attempt success is demonstrated, these results may be utilized to justify the expansion of this model of care as a means of providing enhanced smoking cessation assistance for our veterans at the STVHCS.

**Funding:** n/a

Class of Presentor: Resident
COP Affiliation: Resident

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SURVEILLANCE ULTRASOUND IN THE NEURO INTENSIVE CARE UNIT: TIME TO DEEP VEIN THROMBOSIS DIAGNOSIS

Kristi L. Hargrove, PharmD Colleen Barthol, PharmD, BCPS, Stefan Allen, PharmD, Crystal Franco-Martinez, PharmD, BCPS2029
Department of Pharmacotherapy and Pharmacy Services, University Health System, San Antonio, TX; Pharmacotherapy Education & Research Center, UT Health San Antonio, San Antonio, TX; Division of Pharmacotherapy, UT Austin College of Pharmacy, Austin, TX

Body of Abstract: Purpose: To investigate the value of routine surveillance ultrasound in early deep vein thrombosis (DVT) diagnosis in Neuro Intensive Care Unit (ICU) patients. Routine screening ultrasounds have commonly been performed in Neuro ICU patients admitted for greater than five days. This practice is aimed at early detection and initiation of anticoagulation (AC) to prevent further complications including pulmonary embolism (PE). However, initiating AC for the treatment of asymptomatic DVTs may put patients at higher risk of hemorrhagic events or re-bleed.

Methods: Retrospective chart review of patients diagnosed with DVT during admission to the Neuro ICU at University Hospital from January 1, 2012 through December 31, 2017. Patients were identified through ICD9 and ICD10 codes, screened for study inclusion criteria, then assigned to a symptom-based ultrasound group (control group) vs a surveillance ultrasound group. The primary outcome was time from admit to DVT diagnosis (in hours). Secondary safety outcomes included AC treatment discontinuation secondary to suspected hemorrhage or new or expanding hemorrhage on follow-up head computerized tomography (CT).

Results: A total of 116 patients were identified with 50 included in the venous thromboembolism analysis. Of these patients, 23 were assigned to the control group and 27 to the surveillance group. Seven patients (control = 4, surveillance = 3) were diagnosed with PE without DVT and were excluded from the primary outcome analysis. Time to DVT diagnosis was not statistically different with a median time of 172 hours vs 148 hours (control vs surveillance, respectively, p = 0.2). There was no difference in AC discontinuation rates (control 21.7% (5/23) vs surveillance 11.1% (3/27), p = 0.4). Of the 27 patients with follow-up head CT, two patients in the control group and two patients in the surveillance group showed a new or expanding hemorrhage (p = 1).

Conclusion: Routine surveillance ultrasound did not lead to significantly earlier DVT diagnosis. Safety outcomes of bleeding events were not different between groups when comparing treatment discontinuation or new or expanding hemorrhage on head CT. Utility of surveillance ultrasound in this population should continue to be evaluated in large, prospective trials before routine use can be recommended.

Funding: n/a

Class of Presentor: Resident
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OPTIMIZING BONE MINERAL DENSITY SCREENING AMONG VETERANS WITH OSTEOPOROSIS ON ALENDRONATE

Pamela Ijeoma, PharmD
Michael Gass, PharmD, BCOP
UT Austin College of Pharmacy, Pharmacotherapy Education and Research Center

Body of Abstract: Rationale: Osteoporosis is characterized by an increase in bone resorption in conjunction with an increased rate of bone turnover. Fracture, the most clinically significant manifestation of the disease, is associated with substantial morbidity and mortality. Guidelines recommend an oral bisphosphonate as first-line therapy to improve bone mineral density (BMD) in patients with osteoporosis. Response to treatment is monitored using dual energy x-ray absorptiometry (DXA).

Presently, there is a lack of consensus on the appropriate timing of BMD testing. The Endocrine Society and AACE/ACE guidelines recommend baseline DXA prior to the initiation of pharmacotherapy with repeat DXA every 1 to 2 years until stable. In contrast, the VA/DOD and ACP guidelines recommend against BMD testing during the first 2 and 5 years of treatment respectively.

Objectives: To evaluate the optimal frequency of BMD testing among veterans receiving alendronate 70mg weekly for osteoporosis.

Methods: Veterans initiated on alendronate 70mg weekly from September 1, 2011 to September 1, 2012 were evaluated. Osteoporosis was defined as BMD 2.5 deviations below the mean (T-score ≤ -2.5 SD) or fragility fracture of the hip or spine. The study population was assigned to one of two groups based on the timing of BMD testing, DXA scan ≤ 18 months and DXA scan > 18 months after treatment initiation. The following patients were excluded: creatinine clearance (CrCl) < 35 ml/min, calcium or vitamin D deficiency without supplementation. Treatment failure was defined as a decrease in BMD > 3% from baseline or ≥ 2 fractures while compliant to therapy. Compliance was defined as ≥ 80% adherence to prescription refills.

Study Outcomes: Time to first DXA scan following treatment initiation, decrease in BMD > 3% from baseline, 5-year fracture rate, and proportion of patients with ≥ 2 fractures.

Interim results: 35 patients met eligibility criteria and were enrolled in the study. Baseline characteristics of patients with DXA scan ≤ 18 months and those with DXA scan > 18 months after treatment initiation were similar. Median age was 68 years and 66 years respectively. Median CrCl was 57 ml/min and 48 ml/min respectively. 9% of patients in each group had vertebral fractures at baseline.

Conclusion: Study conclusion will be presented during poster session.

Funding: n/a

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ACUTE ANTIBODY MEDIATED REJECTION TREATMENT IMPACT ON CLASS I AND CLASS II ANTI-HLA ANTIBODIES IN PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS

Elisabeth Kincaide Kelley Hitchman, Reed Hall, Ikuyo Yamaguchi, Barrett Crowther
University Health System, UT Health San Antonio, and UT Austin College of Pharmacy

Body of Abstract: Purpose: Characterize class I and class II anti-HLA donor specific antibodies (DSA) response to acute antibody mediated rejection (AMR) treatment in pediatric kidney transplant recipients (KTR).

Methods: A single-center retrospective chart review of pediatric KTR receiving a renal transplant between 5/1/13 to 9/30/17 was conducted. Patients <18 years old at transplant experiencing first episode of acute AMR and received treatment were included. DSA were identified by single antigen bead Luminex® assays at: time of transplant, acute AMR diagnosis, ~30 days post treatment, and ~90 days post treatment. DSA categorized as weak: 1000 - 2999 mean fluorescence intensity (MFI); moderate: 3000 - 9999 MFI; strong: > 10,000 MFI. Treatment response was defined as MFI decrease ≥30% from diagnosis to ~30 days post treatment.

Results: 62 DSA were identified from 12 patients [25 (40%) Class I and 37 (60%) Class II]. 100% of DSA were treated with IVIG and PP. 50/62 (80%) were treated with rituximab. The same 51/62 (82%) DSA achieving ≥30% MFI reduction also achieved a categorical shift. Univariate analysis revealed 24/25 (96%) class I DSA vs. 27/37 (73%) class II DSA (p=0.0383) achieved a treatment response. Multivariate analysis revealed rituximab (p=0.0041) and lower MFI (p=0.0017) at diagnosis as independent predictors of treatment response. Matched pairs analysis for DSA MFI reduction revealed significant DSA reduction from AMR diagnosis, median 3359 (1527-11,658 IQR) MFI, to ~30 days post treatment, median 604 (239 - 2708 IQR) MFI (p<0.0001). Matched pair analysis between ~30 days- and ~90 days-post treatment revealed no significant difference between these time points for either class I DSA (p=0.21) or class II DSA (p=0.296).

Conclusion: Rituximab and lower MFI at AMR diagnosis were positive predictors of DSA MFI reduction. The same DSA achieved ≥30% and categorical shift, indicating ≥30% is an appropriate AMR treatment target. Treatment resulted in a significant reduction in MFI from AMR diagnosis to 30 days post treatment, without DSA MFI rebound at 90 days. Class I DSA were more likely to respond to treatment. As DSA with higher MFI were less likely to respond to treatment, a more timely AMR diagnosis could improve treatment response.

Funding: n/a

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Abstract 92

DURATION OF DUAL ANTIPLATELET THERAPY AFTER STENT PLACEMENT IN A VETERAN HOSPITAL

Justina Lipscomb PharmD1,2 Ashley Oliver PharmD1, Sarah Rumbellow PharmD1,2, Christopher Frei PharmD1,2, Mark Wong PharmD1, Rene Oliveros MD1

1South Texas Veterans Health Care System
2University of Texas - Austin, College of Pharmacy

Body of Abstract: Introduction: The current acute coronary syndrome (ACS) guidelines recommend that patients with ACS who receive stent placement during percutaneous coronary intervention (PCI) be treated with dual antiplatelet therapy (DAPT). DAPT consists of aspirin and a P2Y12 inhibitor, such as clopidogrel, ticagrelor or prasugrel. Recent studies have demonstrated that high risk patients who tolerate DAPT without bleeding complications may benefit from therapy beyond the recommended duration of at least 12 months. The objective of this study is to assess the cardiocerebrovascular (CVD) and bleeding risk associated with DAPT for more than 12 months (prolonged) vs 12 months or less (standard) after stent placement in a veteran population.

Methods: This is a retrospective chart review of patients on DAPT between 01/01/2013 - 12/31/2013. Patients were excluded if they had documented coagulopathies or allergies to any P2Y12 inhibitor or received CABG for the event.

The primary outcome for this study is the composite of all-cause mortality, stroke, recurrent ACS and stent thrombosis. Secondary outcomes included each individual outcome from the primary composite and bleeding. Major bleeding was defined according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding. Patients were followed for a total of 3 years.

Results: A total of 85 patients are included in data collection, with 36 patients (42%) in the standard group. The prolonged DAPT arm had more patient with diabetes (51% vs 41.7%), dyslipidemia (86% vs 79%), hypertension (87.8% vs 77%), current tobacco use (69.4% vs 66.7%) and CVD (59.2% vs 52.3%). The average time of standard therapy was 8.6 months vs 23.6 months for prolonged therapy. The majority of patients presented with unstable angina (42%) and NSTEMI (38%). Majority of patients took clopidogrel (93%) and the average age is 64. Prolonged therapy led to higher rates of the primary composite outcome (55% vs 36%), recurrent ACS (37.8% vs 16.6%) and bleeding (0.08% vs 0.05%). Rate of overall death was higher in the standard group (16.6% vs 14%). There was no difference in stroke rates and there were 3 occurrences of stent thrombosis, all occurring in the prolonged group.

Conclusion: DAPT longer than 12 months after PCI in a veteran population had higher rates of recurrent ACS and bleed.

Funding: n/a

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Fourteenth Annual Louis C. Littlefield Celebrating Pharmacy Research Excellence Day In Professional, Graduate, and Postgraduate Programs

Abstract 93

ASSESSING PROVIDERS’ KNOWLEDGE OF AND WILLINGNESS TO RECOMMEND PHARMACIST-PROVIDED POINT-OF-CARE PHARMACOGENETICS TESTING

Natalia Malesa1,2, Julie Gould1,2, Jacquelyn Brondo1, Nathan Pope1,2, Carolyn Brown1, Mark Comfort2, Gretta Leckbee 2 -1UT Austin College of Pharmacy, 2H-E-B Pharmacy

Body of Abstract: Background: Use of pharmacogenetics (PGx) testing to personalize drug therapy has shown improved outcomes in certain patients. Point-of-care genotyping assays are accurate and accessible in community pharmacies. Specialized pharmacokinetics knowledge makes pharmacists suited to interpret PGx results and consult with patients and providers to personalize drug therapy. Studies show provider interest in PGx testing but also the need for further education to optimize its use in patient care.

Objective: To assess providers' knowledge of PGx testing and their willingness to recommend point-of-care PGx testing in the community pharmacy setting.

Methods: A survey was administered to providers that assessed their PGx knowledge and willingness to recommend point-of-care PGx testing in the community pharmacy setting. Knowledge (3 items) and willingness (5 items) measures were evaluated using a 5-point Likert scale with 1 representing "Strongly Disagree" and 5 representing "Strongly Agree." Sites were selected for inclusion by correlating usage of drugs with known PGx biomarkers to those prescribed at practices within the Greater Austin area. 207 sites identified by those parameters were randomized and included if willing to participate.

Results: Fifteen providers (n=15) at three sites completed the survey. Providers rated their perceived knowledge of reduced efficacy (3.67 ± SD) and increased adverse effects (3.47 ± SD) caused by certain drug/gene pairs as neutral to agree. Their familiarity with PGx testing (3.07 ± SD) and belief in the benefit of testing (3.33 ± SD) were rated lower. Providers indicated neutrality to disagreement in rating their comfort with recommending testing to patients (2.87 ± SD), the possibility of referring patients to a community pharmacy for testing (2.80 ± SD), their confidence in community pharmacists' ability to interpret results (2.87 ± SD), and their belief that price is appropriate (2.73 ± SD).

Conclusions: At this time, survey results indicate that providers do not feel knowledgeable about PGx and are not poised to recommend or refer their patients to community pharmacies for point-of-care PGx testing. Further education about PGx testing and the role pharmacists might play in this area are warranted.

Funding: The Arlyn Kloesel Endowment for Excellence in Pharmacy Practice

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COMPARISON OF CEFAZOLIN AND CEFTRIAXONE FOR PEDIATRIC URINARY TRACT INFECTION: A RETROSPECTIVE, NON-INFRINGEMENT STUDY

Laura Meadow, PharmD
Kathryn Merkel PharmD, BCPS (AQ-ID), BCPPS; Carolyn Ragsdale, PharmD, BCPS, BCPPS; Ronda Machen, PharmD, RD, BCPPS, BCNSP; Eimeira Padilla-Tolentino, PharmD, PhD
Dell Children's Medical Center

Body of Abstract: Purpose: American Academy of Pediatrics (AAP) guidelines for pediatric urinary tract infections (UTI) recommend treatment with third-generation cephalosporins based on the ability to empirically cover most uropathogens. The literature regarding treatment of UTIs with intravenous first-generation cephalosporins is limited. It is hypothesized that the clinical cure rate of the narrow-spectrum alternative, cefazolin (CFZ), is non-inferior to ceftriaxone (CTX) for pediatric UTIs by a non-inferiority margin of 10%.

Methods: Pediatric patients between 2 months and 18 years of age with fever, pyuria, and urine culture positive for Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis who received CFZ or CTX were retrospectively compared in a single-center non-inferiority study. The primary outcome is a composite of clinical success, defined as defervescence, switch to oral narrow-spectrum antibiotics, or discharge home within 48 hours of first inpatient dose of antibiotics. The secondary outcomes are hospital length of stay (LOS), presence of bacteremia, and readmission for UTI within 30 days of discharge.

Results: Of 166 patients that met inclusion criteria [CFZ (n=32), CTX (n=134)], the majority of pathogens isolated were Escherichia coli (98.8%). The rate of clinical success was achieved for 84.4% (n=27/32) of patients in the CFZ group and 96.3% (n=129/134) of patients in the CTX group, 95% CI of the difference (-0.28, -0.02), p=0.62. Since the confidence interval difference includes -0.10 (the established margin), non-inferiority is not established. Hospital LOS had a median of 39 hours (IQR 25.8, 45.5) for CFZ and 46 hours (IQR 35.0, 64.0) for CTX, HR 0.59, 95% CI (0.40, 0.88), p = 0.01. There were no significant differences for the remaining secondary outcomes: presence of bacteremia and readmission for UTI within 30 days of discharge.

Conclusion: Non-inferiority is not established for the primary outcome. Also, despite the higher clinical success rate of CTX patients, they were about 40% less likely to discharge from the hospital compared to CFZ patients. However the smaller sample size in the CFZ group limits generalizability of results, and a larger study is needed to compare these two groups.

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Body of Abstract: Background: Chemotherapy-induced nausea and vomiting (CINV) can cause complications during chemotherapy treatment. Antiemetics for CINV prophylaxis are based on emetic potential of chemotherapy agents. The emetic potential of carboplatin AUC > 4 was changed from moderate to high. This new classification has a recommendation to use a neurokinin-1 receptor antagonist with a serotonin receptor antagonist and a corticosteroid for CINV prophylaxis. Literature supporting this recommendation is limited to subgroup analysis lacking statistical power to detect differences in CINV control. We hypothesized a success rate for controlled CINV of 75% in both groups based on prior studies. The Seton Healthcare Family antiemetic protocol currently recommends ondansetron and dexamethasone for patients receiving carboplatin.

Objective: Evaluate CINV control in patients receiving carboplatin AUC > 4 vs. irinotecan and oxaliplatin-based chemotherapy regimens.

Methods: This retrospective, single-center equivalence study compared the proportion of adult patients with controlled CINV between carboplatin AUC > 4 and irinotecan or oxaliplatin-based regimens. The CINV control equivalence margin was set at 10% with a required sample size of 322 per group. Controlled CINV was defined as no documented nausea or vomiting, no emergency department visit or hospital admission from CINV, and no use of fosaprepitant.

Results: A total of 127 patients received carboplatin and 208 patients received irinotecan or oxaliplatin. The primary outcome of controlled CINV occurred in 44.9% of carboplatin patients and in 26.0% of irinotecan or oxaliplatin patients. The 90% confidence interval for the difference in CINV control was 0.10-0.28, and because it is not included in (-0.10, 0.10), the two response rates cannot be declared equivalent at the 0.05 significance level. The secondary outcome of fosaprepitant use was significantly less in the carboplatin vs. the irinotecan or oxaliplatin group (8.7% vs. 28.8%).

Conclusions: CINV control in patients receiving carboplatin AUC > 4 compared to irinotecan and oxaliplatin-based chemotherapy regimens was not equivalent. Despite not reaching the required sample size, our data indicates that use of fosaprepitant as part of the first line antiemetic regimen for carboplatin AUC > 4 is likely unnecessary.

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TOLERABILITY OF SACUBITRIL/VALSARTAN IN HOSPITALIZED PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION.

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Body of Abstract: Background: Sacubitril/valsartan (Entresto™) is an angiotensin receptor-neprilysin inhibitor that has emerged as a first-line treatment for heart failure with reduced ejection fraction (HFrEF) due to a significant reduction in death from cardiovascular causes and hospitalization compared to enalapril in the PARADIGM-HF trial. The trial utilized an extensive run-in phase with patients eliminated who could not tolerate sacubitril/valsartan or enalapril. Randomized studies evaluating sacubitril/valsartan were conducted in stable outpatients with chronic HFrEF, while information regarding initiation in hospitalized patients or during HFrEF exacerbations is lacking.

Methods: This retrospective, multicenter, cohort study compared tolerability for hospitalized patients who received sacubitril/valsartan or lisinopril for HFrEF. Patients were included if they had a diagnosis of HFrEF in addition to new initiation of sacubitril/valsartan at any dose or lisinopril 10 mg or less. The primary outcome examined the rate of study drug discontinuation from any cause, while secondary outcomes analyzed adverse events.

Results: A total of 150 patients were identified for study inclusion, which were evenly split between each medication. On average, patients were 58 years old, had an ejection fraction of 24%, and had newly diagnosed HFrEF in 58.7%. Sacubitril/valsartan was discontinued by 16 patients (21.3%) as compared to 5 (6.7%) in the lisinopril group (P = 0.01). The most common reason for discontinuation of sacubitril/valsartan was hypotension while lisinopril was most frequently stopped due to acute kidney injury. A total of 28 patients (37.3%) in the sacubitril/valsartan group had doses withheld for adverse effects compared to 17 (22.7%) for lisinopril. No statistically significant differences were found in rates of hyperkalemia and acute kidney injury.

Conclusions: The initiation of sacubitril/valsartan in hospitalized patients was associated with an increased likelihood of discontinuation from any cause compared to lisinopril. These results suggest careful consideration is needed for initiation of sacubitril/valsartan in hospitalized patients and to possibly consider waiting to start in stable patients.

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Abstract 97

SHORT-TERM EFFECTS OF PROPHYLACTIC CORTICOSTEROID THERAPY IN VENTILATOR-DEPENDENT, PRETERM INFANTS: HYDROCORTISONE VERSUS DEXAMETHASONE

An Nguyen, PharmD Jamie Maze, PharmD, Lea Mallett, PhD, Char Peery, PhD, Niraj Vora, MD, Chanin Wright, PharmD

UT Austin College of Pharmacy, Baylor Scott and White McLane Children's Medical Center, Temple, TX

Body of Abstract: While dexamethasone has been used to shorten intubation time and reduce rates of bronchopulmonary dysplasia in preterm infants who were placed on the ventilator secondary to respiratory distress, its adverse effects have deterred its use, especially at high dose. In recent years, hydrocortisone has emerged as an alternative therapy. The purpose of this study was to compare the efficacy and short-term effects of low-dose dexamethasone versus hydrocortisone as prophylaxis for bronchopulmonary dysplasia in preterm, ventilator-dependent infants. This study was submitted and approved by the Institutional Review Board. Retrospective chart review via an electronic medical record system was utilized to evaluate 140 infants with a gestational age of 25 to 32 weeks, birth weight less than 1500 grams, and who required mechanical ventilation secondary to respiratory distress syndrome between 2015 and 2017. Those with severe congenital neurologic or cardiovascular defects, patent ductus arteriosus treatment with NSAIDs, necrotizing enterocolitis or sepsis prior to steroid use were excluded. Infants who received low-dose dexamethasone (n= 9) or hydrocortisone (n = 6) were compared to each other as well as a control group (n = 112). Primary outcomes included diagnosis of bronchopulmonary dysplasia, time to extubation, mortality and need for home oxygen. Steroids were initiated in more premature (26.4 vs. 28 weeks (p = 0.0044) and lower birthweight (0.8 vs. 0.7 kg (p = 0.0024) neonates. Bronchopulmonary dysplasia was diagnosed in 100% infants in the steroid groups at 36 weeks corrected gestational age compared to 50.89% in the control group. Time to extubation was significantly shorter in the non-steroid group (5 days) than steroid groups (47 days and 35.5 days for dexamethasone and hydrocortisone accordingly). Limitations of the study included small sample size and confounding factors such as comorbidities, varied dosing regimens of hydrocortisone and time of steroid initiation among the groups. In conclusion, there was insufficient evidence to determine the efficacy of hydrocortisone compared to low dose dexamethasone in preventing bronchopulmonary dysplasia. Future prospective studies with larger sample size are warranted to shed more light on the role of steroids for the prevention of bronchopulmonary dysplasia.

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Body of Abstract: Background: The incidence of Streptococcus anginosus group (SAG) bacteremia has been increasing at our institution. No guideline recommendations currently exist for treatment of SAG bacteremia. Beta-lactams have historically been the drug of choice due to predictable in vitro susceptibility to these agents. Other agents, such as fluoroquinolones, are active in vitro and have been used for odontogenic infections caused by SAG. Fluoroquinolones have an advantage over beta-lactams because of the excellent bioavailability of oral formulations. However, limited clinical data exist regarding their use in bacteremia. This study's primary objective was to compare treatment failure in patients with SAG bacteremia who were treated with beta-lactam versus fluoroquinolone therapy.

Methods: This was a single-center, retrospective study of patients >18 years of age who had at least one positive SAG blood culture and received either beta-lactam or fluoroquinolone therapy. Patients with polymicrobial bacteremia and multiple antibiotics active against SAG were excluded from analysis. The primary outcome was treatment failure: a composite endpoint of recurrence of bacteremia within 30 days of treatment initiation, 30-day readmission from end of therapy for an infectious complication, and in the fluoroquinolone group, a switch back to a beta-lactam antibiotic.

Results: Thirty-seven patients were evaluated. The hepatobiliary system was the most common identifiable source of SAG bacteremia. The median duration of therapy was 25 days (range, 4 to 58). Treatment failure occurred in 10% of patients (1/10) treated with a fluoroquinolone and 7% of patients (2/27) treated with a beta-lactam. One fluoroquinolone-treated patient and two beta-lactam-treated patients experienced a 30-day readmission for an infectious complication. Two patients in the beta-lactam group died within 30 days of treatment initiation.

Conclusion: Treatment failure was similar between patients receiving a beta-lactam or a fluoroquinolone for the treatment of S. anginosus group bacteremia. However, a larger study is needed to confirm these findings.

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EVALUATION OF MANAGEMENT OF SKIN SOFT TISSUE INFECTIONS IN THE INPATIENT SETTING

Cameron Stuart Pickard, Pharm.D.1,2 Chelsea Kristel Sanchez, Pharm.D., BCPS1,3, Jason Michael Corbo, Pharm.D., BCPS, BCGP1,3

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Body of Abstract: Skin and soft tissue infections (SSTIs) are among the most common infectious diseases necessitating hospitalization and antibiotic treatment. SSTIs lead to an estimated 3.4 million emergency department visits annually, with 13.9%, or 472,600, resulting in subsequent hospitalization. Given the high incidence of SSTIs, as well as the consequences of inappropriate antibiotic use, identifying areas for optimization of skin and soft tissue infection (SSTI) treatment is prudent. Numerous evaluations outside of the Veterans Health Administration (VHA) have documented suboptimal antibacterial use for SSTIs. The primary objective of this medication use evaluation (MUE) is to assess the proportion of Veterans hospitalized with SSTIs whose empiric antibiotic selection and total treatment duration was concordant with the current Infectious Diseases Society of America (IDSA) guidelines. Secondary objectives include describing antibiotic use in patients receiving therapy not in accordance with IDSA guidelines and the corresponding relevant outcomes.

Methods: Initially, Pharmacy Benefits Management VAMedSAFE in collaboration with Veterans Affairs (VA) Salt Lake City IDEAS Group identified SSTI diagnosis codes associated with inpatient visits occurring between June 1, 2016 and May 31, 2017. VAMedSafe generated patient lists for chart review by individual sites. Each site performed a retrospective chart review of patients included on the list. The South Texas Veterans Health Care System (STVHCS) review consisted of 150 patients. Variables collected included demographics, relevant comorbidities, classification and location of SSTI, vital signs, laboratory values, antibacterial allergies, and relevant clinical outcomes for the management of SSTIs as detailed in the objectives.

Results: Results from the STVHCS will be presented during the poster session. Descriptive statistics will be utilized to summarize demographics. Calculations of MUE indicators will be performed.

Conclusion: This MUE represents an effort by the VHA to evaluate the use of antibiotics for SSTIs at various VA sites. An Antimicrobial Stewardship Task Force prototype policy addressing areas for optimization of antimicrobial use based on the MUE results will be developed in addition to targeted education.

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Abstract 100

COMPARISON OF CLOPIDOGREL AND TICAGRELOR USE IN VETERANS RECEIVING PERCUTANEOUS CORONARY INTERVENTION (PCI) AFTER ACUTE CORONARY SYNDROMES (ACS)

Sarah A Rumbellow, PharmD; Ashley Oliver, PharmD; Justina A Lipscomb, PharmD; Mark J Wong, PharmD; Christopher R Frei, PharmD, MSc; Rene A Oliveros, MD
Affiliation: UT Austin College of Pharmacy, South Texas Veterans Health Care System

Body of Abstract: Rationale: ACS are associated with increased mortality. Guidelines for ACS recommend medication management and currently prefer ticagrelor over clopidogrel based on favorable cardiocerebrovascular outcomes of the PLATO trial. However, findings were not significant in patients over seventy-five. The older, more complex veteran population has increased risk for ischemic and bleeding events. Thus, investigation into best practices for this population is warranted. Our study compares the safety and effectiveness of clopidogrel and ticagrelor in veterans with ACS and PCI.

Methods: A retrospective review of electronic medical records was completed. Veterans 18 years and older receiving PCI for ACS initiated on clopidogrel or ticagrelor between January 1, 2013 and November 30, 2016 were included. Patients with coagulopathies, allergy or intolerance to either agent, coronary artery bypass grafting at time of agent initiation, or switched between antiplatelet agents without adverse events were excluded.

The primary outcome is a composite of all-cause mortality, ischemic and hemorrhagic stroke, recurrent myocardial infarction, stent thrombosis, mild, moderate, and severe or life-threatening bleeding based on Global Strategies to Open Occluded Arteries definitions, gastrointestinal bleeding, and bleeding leading to hospitalization. Secondary outcomes include each individual endpoint from the composite.

Results: Preliminary results indicate that groups were similar at baseline. Numerically, more patients in the ticagrelor group had a history of coronary artery disease (CAD) or aspirin use at baseline, but this was not statistically significant. Overall, 98.2% were male and a majority had a history of hypertension or dyslipidemia. Most received aspirin prior to ACS event. About half had a history of diabetes, CAD, or tobacco use. Patients received a median of 385 days of antiplatelet treatment following ACS. The composite outcome occurred in 39.75% of the clopidogrel group compared to 35.0% in the ticagrelor group. There was no statistically significant difference in outcome between groups.

Conclusion: Veterans experiencing ACS with PCI treated with ticagrelor have no difference in risk of experiencing the composite outcome when compared to similar patients treated with clopidogrel.

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DESMOPRESSIN FOR THE STABILIZATION OF INTRACRANIAL HEMORRHAGE IN PATIENTS ON ANTIPLATELET THERAPY

Kyllie S. Ryan-Hummel Crystal Franco-Martinez, Darrel Hughes, Colleen Barthol
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The University of Texas at Austin College of Pharmacy, Austin, Texas

Body of Abstract: Purpose: Acute intracranial hemorrhage (ICH) expansion occurs in approximately 73% of patients, with significant hemorrhage growth occurring in 30-40% of patients within the first 24 hours. ICH expansion is more common in patients taking antithrombotic agents. Guidelines for reversal of antithrombotics in ICH suggest a single dose of desmopressin (DDAVP) 0.4 mcg/kg intravenously for treatment of aspirin/cyclooxygenase-1 inhibitor-associated ICH in addition to platelet transfusion in patients undergoing neurosurgical intervention. Literature to support these recommendations provides conflicting evidence. The primary objective of this study is to determine whether the administration of DDAVP is associated with stabilization of ICH size in patients receiving antiplatelet therapy.

Methods: Single center, retrospective chart review of adult patients with spontaneous or traumatic ICH receiving antiplatelet therapy. Patients were admitted to University Hospital between January 1, 2012 and September 30, 2017 and assigned to one of two groups, DDAVP or no-DDAVP.

Results: A total of 150 patients met inclusion criteria, with 75 patients in the DDAVP group and 75 in the no-DDAVP group; 57% of patients were male with a median age of 72 years [IQR 63-79] and median weight of 73.8 kg [IQR 63.5-86.1]. Traumatic injuries accounted for 69% of the ICHs. The median dose of DDAVP was 0.34 mcg/kg [IQR 0.29-0.39]. Hemorrhage stabilization occurred in 87% vs 71% of DDAVP and no-DDAVP group respectively (p=0.02); however, mortality rates were higher in the DDAVP versus no-DDAVP group (14% vs 5%; p=0.047). One patient in the DDAVP group experienced a venous thromboembolism.

Conclusion: Patients who received DDAVP had greater hemorrhage stabilization, but higher mortality rates compared to those who did not receive DDAVP. This occurrence may not be directly attributable to the DDAVP but could be multifactorial and closely related to patient severity of illness at baseline. The current study adds to the sparse existing literature and further highlights the need for larger, randomized, prospective clinical trials to determine the efficacy and safety of DDAVP for ICH stabilization in patients on concurrent antiplatelet therapy.

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PATIENT EXPERIENCE WITH CLINICAL PHARMACIST SERVICES IN TRAVIS COUNTY FEDERALLY QUALIFIED HEALTH CENTERS

Jennifer Shin, Jamie Barner, Aida Garza, Sara Linedecker, Leticia Moczygemba, Maaya Srinivasa
CommUnityCare Health Centers and University of Texas at Austin College of Pharmacy

Body of Abstract: Rationale: A positive patient experience with care has been linked with good health outcomes. This study seeks to examine patient experience with clinical pharmacist visits in an ambulatory care setting. The study objective is to describe patient experience with services routinely completed for every pharmacist visit, including medication reconciliation, assessment of progress toward treatment goals, medication and disease education, and follow-up instructions.

Methods: This is a cross-sectional, multi-clinic study. Patients > 18 years of age who are, English or Spanish speaking, and have completed a clinical pharmacist appointment will be included. Patients with co-visit appointments (joint physician and pharmacist visits) will be excluded. Patients will evaluate their experience with their visit through a questionnaire comprised of four domains: pharmacists' communication skills, patients' understanding of medications, patients' understanding of health conditions, and patient understanding of follow-up instructions. Demographic and health-related variables will also be collected (age, gender, race, health condition(s) and perceived health status). Patients will indicate their level of agreement for each question using a 5 point Likert scale from 1="strongly disagree" to 5="strongly agree". The primary outcome will be an overall score on the experience of the visit. Secondary outcomes will include patient scores on each domain. Clinical pharmacists at selected clinics will conclude each visit with offering the opportunity to participate in the survey. Results of the study will be analyzed with descriptive and inferential statistics, as well as Cronbach’s alpha for scale reliability.

Results: Data will be collected and analyzed once the study duration ends.

Conclusion: It is expected that the study findings will provide information about patients' experience with clinical pharmacist services and whether there are opportunities for improvement.

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COMPARATIVE SAFETY AND EFFICACY OF CONTINUOUS INFUSION AND INTERMITTENT BOLUS NEOSTIGMINE FOR ACUTE COLONIC PSEUDO-OBSTRUCTION

Lucas W. Smedley Dana G. Boeck; Colleen A. Barthol; G. Christina Gutierrez, UT Austin College of Pharmacy, University Health System, University of Texas Health Science Center at San Antonio, San Antonio, TX

Body of Abstract: Purpose: To compare clinical response of intermittent bolus versus continuous infusion neostigmine for acute colonic pseudo-obstruction (ACPO). ACPO occurs due to reduced colonic parasympathetic activity. Neostigmine is an acetylcholinesterase inhibitor which increases smooth muscle contraction frequency by increasing acetylcholine at autonomic nervous system synapses. Neostigmine has been studied for treatment of ACPO as an intermittent bolus and continuous infusion, but the two modalities have never been compared.

Methods: This single-center, retrospective study compared intermittent bolus versus continuous infusion neostigmine for ACPO between January 1, 2006 and August 31, 2017. Pharmacy charges for neostigmine were used to identify patients and data points were collected from the electronic medical record. The primary outcome was initial clinical response, defined as bowel movement (BM) within 4 hours of bolus dose or 24 hours of initiation of continuous infusion. Secondary outcomes included time to BM, number of patients with bowel diameter reduction at 24 hours, need for additional courses of neostigmine or colonic decompression/surgical intervention, and bradycardia incidence.

Results: Seventy-five patients were included (37 in bolus group and 38 in continuous infusion group). Mean total neostigmine dose in the first 24 hours was 2.6 ± 1.9 mg in the bolus group and 8.9 ± 3.0 mg in the continuous infusion group. Rates of initial clinical response were similar between groups (62.2% in bolus group and 81.6% in continuous infusion group, p = 0.06), but patients in the bolus group were less likely to have reduction in bowel diameter (34.9% vs. 65.1%, p = 0.004). Patients in the bolus group had a shorter time to BM (1.4 hrs vs. 3.5 hrs, p = 0.0478), but were more likely to require nasogastric decompression after therapy (67.6% vs 39.5%, p = 0.0148). Patients in the bolus group were less likely to experience bradycardia (13.5% vs 39.5%, p = 0.011) but there was no difference in atropine requirement (10.8% vs 5.26%, p = 0.43).

Conclusion: Initial clinical response following intermittent bolus neostigmine was similar to that of continuous infusion, with a shorter time to bowel movement. Patients who received continuous infusion had a greater incidence of decreased bowel diameter but higher rates of bradycardia.

Funding: n/a

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IMPLEMENTING HIV PHARMACY SERVICES WITHIN A REGIONAL RETAIL COMMUNITY PHARMACY ORGANIZATION: DEFINING CRITERIA TO EFFECTIVELY AND EFFICIENTLY IMPLEMENT.

Daniel A. Tapia, Pharm.D.1,2, Beatriz Ugalde, Pharm.D.1,2, Nathan D. Pope, Pharm.D.1,2, Leticia R. Moczygemba, Pharm.D., Ph.D., Jennifer Willbanks, Pharm.D.2, James Weems, R.Ph.2, & Donna Montemayor, R.Ph.2
Affiliation: 1The University of Texas at Austin College of Pharmacy, 2H-E-B Pharmacy

Body of Abstract: Currently, there is no model for implementing HIV specialty pharmacy services within a non-specialty community pharmacy workflow. This study aims to describe the criteria for selection of community pharmacy locations that will participate in a specialty HIV clinical program within H-E-B pharmacy, and to describe the process of integrating specialty pharmacy services into the workflow of a community pharmacy. H-E-B pharmacies serve patients throughout South Central Texas and are organized by regions including: Central Texas, San Antonio/West Texas, Gulf Coast, Border, and Houston. One pharmacy from each region will be selected to manage all HIV prescriptions for its respective region and provide enhanced HIV pharmacy services which include individualized calls and counsels, as well as monthly refill reminders to promote adherence and minimize adverse effects. The H-E-B specialty workflow was examined and compared to the non-specialty pharmacy workflow. Different community pharmacy continuing education programs were evaluated to identify a training program for pharmacists. Offsite prescription fulfillment capacity and pharmacy productivity was assessed and full time equivalents were determined for technicians and pharmacists. The distribution of HIV scripts and HIV prevalence were analyzed and contrasted, and prescriber patterns were assessed within each county served by H-E-B Pharmacy.

Based on the above information, the HIV specialty services should only be considered at pharmacies which are located in counties congruent with moderate to high HIV prevalence, high HIV prescription fill rates, and high prescribing activity, and whose pharmacists are willing to deliver enhanced HIV pharmacy services. Pharmacy locations that should not be considered for this service include those with an average weekly prescription number ≥ 3500, located in counties with low HIV prevalence and low HIV prescription rates, and have limitations of physical space and networking infrastructure to allow expansion of resources and services.

Implementation of this practice model can be applied to various community pharmacies to create similar HIV specialty focused pharmacies. Prescriber relationships, pharmacy training and expansion of resources promote sustainability and adaptability of the center.

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IMPACT AND FEASIBILITY OF IMPLEMENTING A SYSTEMATIC APPROACH FOR MEDICATION THERAPY MANAGEMENT IN THE COMMUNITY PHARMACY SETTING: PILOT STUDY EXPANSION

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Marie Tillema Murray, PharmD, Preceptor and Community Pharmacist with H-E-B Pharmacy

Body of Abstract: The purpose of this study is to determine if expansion of a systematic approach to providing medication therapy management (MTM) as part of the pharmacy workflow has an impact on completion rates of comprehensive medication reviews (CMRs) and targeted intervention program (TIPs). This study will also assess pharmacists’ perceptions regarding the feasibility of and barriers to the process.

This process improvement study included thirty-seven grocery store-based community pharmacy sites with variable MTM completion rates, MTM opportunities, and prescription volume. Training for pharmacists and technicians involved online tutorials in the form of a one hour webinar and in-person training to assess understanding with resources for documentation. Technicians prepare MTM paperwork, including a standardized CMR worksheet, which pharmacists use to deliver the service face-to-face at the counsel window. Outcomes measured over a 12 month period include: change in CMR completion rate from pre-implementation (June 2017-November 2017) to post-implementation (December 2017-May 2018); change in TIP completion rate from pre- to post-implementation and pharmacists' assessment of barriers and feasibility. Data will continue to be assessed utilizing descriptive statistics with paired t-tests evaluating the change in completion rates from pre- to post-implementation.

A previous pilot study assessed pre- and post- completion rates over a four month period at four sites. Primary outcomes showed statistically significant increases in CMR completion rates from 2.7%±5.4% to 23.2%±7.7% respectively (p<0.10). Secondary outcomes were also significant with TIP completion rates increasing from 3.4%±4.2% to 24.9%±19.2% respectively (p<0.10). Continuation of this systematic approach with expansion to thirty-seven sites as well as online training should result in higher significance of CMR and TIP completion rates. The overall implications of this study can illustrate effective integration of MTM into pharmacy workflow across various community pharmacy settings. This new systematic process of MTM can additionally lead to improvement in patient outcomes, CMS quality measures, and positively depict the expanding roles of pharmacist and technicians.

Funding: n/a

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OUTPATIENT MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROME IN THE EMERGENCY DEPARTMENT: A PILOT PROJECT

Samantha M. Vogel, PharmD, Tawny Smith, PharmD, BCPP

Background: Medically assisted detoxification with benzodiazepines for alcohol withdrawal syndrome (AWS) has typically been performed in the inpatient setting. However, patients who present with mild-to-moderate AWS may be managed in the outpatient setting. Positive results with gabapentin-based outpatient detoxification have been reported. A gabapentin-based outpatient protocol offers the potential for reduced hospital costs, decreased lost work days, and reduced risk of relapse associated with benzodiazepine use.

Objectives: This pilot project aims to 1) provide clinician education on non-benzodiazepine treatment of alcohol withdrawal, 2) develop and implement a three-month pilot of an alternative gabapentin-based outpatient alcohol detoxification protocol, and 3) assess changes in prescribing and psychosocial practices before and after clinician education and protocol availability.

Methods: This is a pre-post pilot project. Patients who present with AWS to the emergency department (ED) of Dell Seton Medical Center will be considered for inclusion. Patients presenting within three months prior to clinician education and protocol implementation will be categorized as the pre-protocol group. Patients presenting within three months following clinician education and protocol implementation will be categorized as the post-protocol group. Demographics, AWS variables, and hospital demographics will be collected for all subjects. Patients will be assessed for prescribing practices and treatment related outcomes (prescription information including changes in benzodiazepine and gabapentin prescribing, use of adjunctive treatment, psychosocial interventions, referral for inpatient admission, ED visits or admissions for AWS within 30 days of discharge). Implementation of the pilot is pending approval by overseeing committees within our healthcare system.

Outcomes: We will report number and percent of demographic and AWS variables for all patients who meet inclusion criteria. We will report number and percent of treatment-related outcomes, including medication management information, for subjects in both the pre-protocol and post-protocol groups.

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ANTIDEPRESSANT ADHERENCE IN PRIMARY CARE PATIENTS DURING THE ACUTE TREATMENT PHASE: A QUALITY IMPROVEMENT PROJECT TO ADDRESS MDD43H

Raeschell Williams, PharmD, MPH Jana Shults, PharmD, BCPP; Holly Winkler, PharmD, BCPP
Affiliation: 1. Pharmacy Department, South Texas Veterans Health Care System, San Antonio, TX 2. Pharmacotherapy Division, College of Pharmacy, The University of Texas at Austin, Austin, TX

Body of Abstract: Depression impacts approximately 15 million American adults each year. One of the biggest predictors for successful management of depressive symptoms is adherence to antidepressant therapy. Literature suggests that a longer treatment duration may increase the proportion of patients who will achieve response or remission. The purpose of this quality improvement project is to improve patient adherence to antidepressant therapy during the first 114 days of treatment for patients enrolled in a clinic that utilizes Primary Care Mental Health Integration Clinical Pharmacy Specialists (PCMHI CPS). This project is a prospective pre- and post-evaluation utilizing the Department of Veterans Affairs Antidepressant Non-Adherence Report (mdd43h) and South Texas Veterans Health Care System (STVHCS) electronic medical records. Patients may be enrolled in any of the outlying primary care clinics within STVHCS. PCMHI CPSs contact the patients within their respective clinics who are identified as non-adherent to their antidepressant as identified through mdd43h reports. The CPSs will discuss reasons for non-adherence, to include medication side effects, intolerability, forgetting to refill the medication, etc. When contacted, the CPS will document in the electronic medical record their conversation with the patient and the steps taken to address the non-adherence, including refilling the medication, changing the medication to a 90-day supply, discontinuing the medication, re-engaging the patient in mental health services, or other interventions. Patient demographic information, clinic location, primary care provider, and the pharmacist intervention will be recorded for study purposes. The primary outcome is to decrease the antidepressant non-adherence rate by 5% from baseline by March 31, 2018. Secondary outcomes include assessing patient-reported barriers to refilling medications and discovering places for intervention, analyzing non-adherence rates by clinic, analyzing non-adherence rates by provider, analyzing the time to reach the primary outcome, and evaluating the impact of interventions on clinical workload. At the time of abstract submission, 116 patients were contacted. The data and results of this quality improvement project will be presented during the poster session.

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Abstract 108

THE IMPACT OF WEIGHT-BASED MELPHALAN DOSING STRATEGIES IN AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT FOR MULTIPLE MYELOMA

Erin Yeung, PharmD, BCPS  John Malamakal, PharmD, BCPS, BCOP

UT Austin College of Pharmacy, South Texas Veterans Health Care System

Body of Abstract: Over one-third of Americans are obese, but minimal guidance exists for weight-based drug dosing in the setting of obesity. The American Society of Bone Marrow Transplant (ASBMT) released obesity guidelines in 2014 that recommend the use of actual body weight (ABW) to calculate melphalan (MEL) conditioning doses while acknowledging the lack of quality evidence to make strong recommendations. At the South Texas Veterans Health Care System (STVHCS), adjusted body weight (AdjBW) is used instead of ABW to calculate MEL doses in patients weighing over 20% of their ideal body weight. This study compares autologous hematopoietic stem cell transplant (autoHSCT) outcomes in multiple myeloma (MM) patients receiving MEL conditioning at STVHCS. Potential differences in toxicity or outcomes may help determine optimal dosing practices based on ABW or AdjBW.

This is a retrospective, single-center study using the STVHCS transplant database and electronic medical record to perform a historical chart review on MM patients receiving MEL conditioning regimens for autoHSCT from January 1, 2012 to January 1, 2015. Patients with history of previous HSCT or planned tandem autoHSCT transplant were excluded. The primary outcome is 3-year progression free survival (3yr PFS). Secondary outcomes included 3-year overall survival (3yr OS).

Of the 149 patients included, 43 patients received MEL dosed by ABW and 106 patients received MEL dosed by AdjBW. Both groups were well-balanced, but more patients achieved a complete response (CR) prior to transplant (19% vs 4%, p=0.003) in the ABW group. The rate of 3yr PFS was 44% vs. 43% in the ABW and AdjBW groups, respectively (p=0.930), with a median time to progression of 641 days vs. 656 days (p = 0.435). The rate of 3yr OS was 67% vs. 78% in the ABW and AdjBW groups (p = 0.164). Median time to death was not reached. More patients in the ABW group achieved a CR at 100 days post transplantation (21% vs 6%, p=0.005) but experienced more grade 3/4 nausea/vomiting (16% vs. 5%, p=0.009). Results were limited by small sample size, retrospective design, and lack of statistical significance.

Dosing based on AdjBW instead of ABW in obesity may be an acceptable dosing strategy with similar transplant outcomes and less toxicity. Adequately powered prospective studies are warranted to confirm these findings.

Funding: n/a

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A COMPARISON OF INJECTABLE DIAZEPAM AND LORAZEPAM IN THE GOAL-DIRECTED MANAGEMENT OF SEVERE ALCOHOL WITHDRAWAL

Daria Zavgorodnyaya, PharmD Emily K. Hodge, PharmD, BCCCP; Lawrence H. Brown, PhD; Mitchell J. Daley, PharmD, FCCM, BCPS
Affiliation: Dell Seton Medical Center at University of Texas

Body of Abstract: Background: Alcohol withdrawal syndrome (AWS) affects over fifty percent of individuals with alcohol use disorder. Benzodiazepines prevent the most feared complications of AWS, seizures and delirium tremens, and are the treatment of choice. Diazepam (DZP) and lorazepam (LZP) are the two most commonly utilized agents within the class, but evidence on their comparative efficacy is limited. The purpose of this study was to compare injectable DZP and LZP in the treatment of severe AWS.

Methods: This was a multi-center, retrospective cohort study of adult patients admitted to an intensive or intermediate care unit with the primary diagnosis of AWS from March 1, 2014 to October 31, 2017 who received at least 12 milligrams of LZP equivalents within 24 hours of initiation of severe AWS protocol. The primary outcome was the number of hours with Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) scale scores at goal over the first 24 hours of treatment. Secondary outcomes included total benzodiazepine requirement; total number of benzodiazepine doses; time until discontinuation of protocol; need for adjunct therapy; study drug costs, length of stay; mortality; and adverse events.

Results: A total of 193 patients were included (LZP [n=102]; DZP [n=91]). Time with CIWA-Ar scores at goal within the first 24 hours was higher in the LZP group (LZP 14 h [IQR 10-17] vs. DZP 12 h [IQR 9-15]; p=0.04). Patients in the LZP group required fewer number of doses at 24 hours (LZP 10 doses [IQR 7-14], vs. DZP 13 doses [IQR 9-19]; p=0.02), but total cumulative LZP equivalents were similar at 24 hours (LZP 32 mg [IQR 19-56], vs. DZP 40 mg [IQR 22-79]; p=0.06) Time until protocol discontinuation was longer in the LZP group (LZP 79.9 h [IQR 53.0-112.8], vs. DZP 70.4 h [IQR 46.1-99.5]; p=0.04). Drug cost at 24 hours was higher in the DZP group (LZP $8.0 [IQR 4.6-14.0] vs. DZP $204.5 [IQR 112.5-404.1]; p<0.01) There were no differences between the groups for other pre-specified outcomes.

Conclusion: As compared to DZP, patients who received LZP for the treatment of severe alcohol withdrawal had more time with CIWA-Ar at goal during the first 24 hours. Overall, efficacy and safety outcomes appeared similar between the groups. Based on our findings coupled with the high cost of injectable DZP, LZP is recommended for the initial treatment of severe AWS.

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Abstract 110

EFFECTS OF PHARMACIST-LED MANAGEMENT OF LONG-ACTING OPIOIDS IN PRIMARY CARE WITHIN VETERAN HEALTH CARE SYSTEM: RETROSPECTIVE AND PROSPECTIVE CHART REVIEW

LiChao Zhao, PharmD
Shuang Ouyang, PharmD, BCPS, BCPP
Affiliation: UT Austin College of Pharmacy, Pharmacotherapy Education & Research Center

Body of Abstract: Background: Chronic pain is a significant health issue, affecting an estimated 100 million Americans, or one third of the U.S. population. Over the past 30 years, there have been major shifts in the use of opioid therapy (OT), with chronic pain management becoming synonymous to long-term opioid therapy (LOT) since the 1990s. The 2016 CDC guidelines contained recommendations for lower daily opioid dosages to manage chronic pain and combat the increase in current opioid-related mortalities. Thus, some patients who are tapered rapidly may be left with uncontrolled pain, with some resort to illicitly-obtaining opioids. In parallel with the national effort to address the drug overdose epidemic, clinical pharmacists could play a unique role as pain management experts to help in improving the care of patients experiencing chronic pain. Further studies should be conducted to investigate the potential benefit of involving clinical pharmacists in pain management to reduce barriers to care and its effect on improving chronic pain control.

Objective: To assess the efficacy and impact of pharmacist-led chronic pain management of patients prescribed long-acting opioids in the primary care setting.

Design, Setting, and Methods: The evaluating team conducts chart reviews to determine the eligibility of patients currently on the fentanyl transdermal patch for medication management with a pain clinical pharmacy specialist (CPS). This study compares the care received pre- and post- CPS intervention(s) at the South Texas Veterans Health Care System. The primary outcome is the number of encounters for services referred by pharmacist-led interventions. Secondary outcomes include Morphine Equivalent Daily Dose (MEDD), average pain score, quality of life function, and number of responses by providers.

Results: From January 2018 to March 2018, 57 patients were included in the evaluation, of which 35 underwent chart reviews. Patients who were excluded include those no longer on a fentanyl patch (n=4), those with previous or existing interactions with a Pain PharmD (n=5), deceased individuals (n=2), persons with an active cancer/enrolled in Palliative Care (n=7), and current CHOICE patients (n=4). Remaining results/data will be presented during poster session.

Conclusion: Results/data will be presented during poster session.

Funding: n/a

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IMPACT OF DISPENSING DISCHARGE MEDICATIONS TO PATIENTS WITH HEART FAILURE, ACUTE MYOCARDIAL INFARCTION, OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION: EFFECT ON 30-DAY ALL-CAUSE READMISSION RATES

Kajia Zheng, Charlotte Farris, Sarah Westbrook, Alejandra Ibarra
Scott and White Medical Center - Temple, Temple, TX

Body of Abstract: Purpose: A key aspect of improving outcomes in patients with heart failure, acute myocardial infarction, and chronic obstructive pulmonary disease (COPD) is ensuring medication adherence. One proposed method to increase medication adherence and decrease readmission rates is to dispense medications to patients on hospital discharge. The purpose of this study is to determine the impact of providing discharge medications for patients with heart failure, acute myocardial infarction, or COPD on all-cause 30-day readmissions.

Methods: A retrospective chart review was completed for patients admitted for a heart failure exacerbation, acute myocardial infarction, or COPD exacerbation receiving their discharge medications through the Scott and White outpatient pharmacy bedside delivery service. The primary outcome was all-cause 30-day readmission rate of studied patients. Secondary outcomes included: all-cause 30-day readmission rates for each individual condition - heart failure exacerbation, acute myocardial dysfunction, and COPD exacerbation.

Results: 8348 patients who received bedside medication delivery through the Scott and White outpatient pharmacy were reviewed. A total of 229 patient encounters met inclusion and exclusion criteria and were included in the study. The all-cause 30-day readmission rate was 26.64%. All-cause 30-day readmission rates was 27.91% (24/86) for patients with heart failure exacerbation, 23.29% (17/73) for patients with acute myocardial infarction, and 28.57% (20/70) for patients with COPD exacerbation.

Conclusion: This study did not show a decrease of all-cause 30-day readmission rates in patients with heart failure exacerbation, acute myocardial infarction, or COPD exacerbation who received bedside medication delivery through the Scott and White outpatient pharmacy. Further studies are needed to elucidate benefits of providing bedside medication delivery on 30-day readmission rates.

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SOLAR ULTRAVIOLET (SUV) IRRADIATION-DEPENDENT ACTIVATION OF IFNGAMMA/STAT1 PATHWAY IN THE EPIDERMIS IS REQUIRED FOR KERATINOCYTE PROLIFERATION AND INFLAMMATION

Nicholas Blazanin, Tianyi Cheng, Steve Carbajal, John DiGiovanni

**Body of Abstract:** Activation of IFNγ/STAT1 signaling in the epidermis is known to affect skin tumor promotion using the mouse two-stage skin carcinogenesis model. However, the role of IFNγ/STAT1 signaling in response to solar ultraviolet (SUV) light is not known. Here we used total and epidermal-specific knockout mouse models to address the role of IFNγ/STAT1 signaling in response to SUV. SUV treatment was characterized by basal keratinocyte hyperproliferation, acanthosis (epidermal thickening), and inflammation. In the mouse epidermis, STAT1 phosphorylation was also observed on both tyrosine (Y701) and serine (S727) residues and this was associated with increased levels of interferon regulatory factor 1 (IRF1) in response to SUV treatment. Using IFNγR (-/-) mice exposed to SUV irradiation, we found a significant reduction in STAT1 phosphorylation and IRF1 levels in the mouse epidermis as well as reduced expression of inflammatory chemokines including Cxcl9, Cxcl10, and Cxcl11. Furthermore, using an IFNγ reporter mouse model system, we demonstrate that CD3+ T-cells located within the epidermis are the likely source of IFNγ production following SUV treatment. Treatment of cultured epidermal keratinocytes with IFNγ caused STAT1 phosphorylation and increased inflammatory chemokine expression confirming results in vivo. SUV treatment of STAT1 (-/-) and epidermal-specific STAT1 (-/-) mice significantly reduced IRF-1 levels and Cxcl9, Cxcl10, and Cxcl11 chemokine expression similar to IFNγR (-/-) mice. Finally, epidermal-specific STAT1 (-/-) mice exhibited reduced epidermal thickening and proliferation in response to SUV irradiation. Taken together, these results suggest a critical role for IFNγ and epidermal STAT1 activation in response to SUV and this pathway could be a novel skin cancer chemoprevention target.

**Funding:**

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Abstract 113

NANOTECHNOLOGICAL APPROACHES INTENDED TO TREAT SKIN CANCER

Clara Luisa Domínguez-Delgado Zubia Akhtar, Godfrey Awuah-Mensah, and Hugh D. C. Smyth

Division of Molecular Pharmaceutics and Drug Delivery, The University of Texas in Austin, 2409 University Avenue, Austin, Texas 78712, USA.

Body of Abstract: Skin cancer is, according to the World Health Organization, the most common malignant disease found particularly in Caucasians. There are many treatment options such as a radical excision, cryotherapy, curettage and electrodessication, radiotherapy, chemotherapy, and diathermia. However, conventional drug delivery systems (DDSs) are often accompanied by systemic unwanted side effects that are mainly attributable to their nonspecific biodistribution and uncontrollable drug release characteristics. Functionalized nanomaterials, particularly, polymeric nanoparticles (NPs) can increase the target specificity as well as the uptake and selective accumulation near a tumour and provide a drug combination therapy, drug release control, and real time monitoring with the goal being to diminish unwanted side effects and their severity, achieving a cheaper treatment and a generally more efficient chemotherapy. Furthermore, drugs of these carriers could be protected from a wide range of factors (pH changes, ionic strength, enzymatic activity, etc.). In this sense, in this study was developed and optimized 1) a modification of nanoprecipitation method to produce pH sensitive polymeric nanoparticles by using different polymers/solvents as stabilizers; 2) and a modification of emulsion-diffusion method to produce nanoparticles using different solvent blends to be used with more hydrophobic polymers and drugs and; 3) An experimental design for this last method was achieved to determine the space design in which nanoparticles can be formed. NPs average size, polydispersity index (PDI), and Z potential analysis were determined by photon correlation spectroscopy. Interesting results were obtained with a blend of A-D polymers used as stabilizers. Compound D was able to decrease the size and the polydispersity index. Z potential did not show a trend, but it was positive and enough high. Similar results were found with NPs prepared by a modification of emulsion-diffusion process, the particle size decreased as decreased the PDI by increased the drug and polymer solubility. Z potential was negative for systems with particles sizes smaller than 1000 nm. It is expected to provide a simplest method alternative to produce nanoparticles that can be used to treat skin cancer.

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Class of Presentor: PostDoc
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ETHANOL INDUCES INCREASE IN EXTRACELLULAR NOREPINEPHRINE IN THE RAT BASAL FOREBRAIN

Saul Jaime, Rueben Gonzales
UT Austin College of Pharmacy, Division of Pharmacology and Toxicology

Body of Abstract: In the current study we sought to quantify the effects of ethanol on extracellular norepinephrine in the rat basal forebrain. We hypothesize an ethanol induced increase in the extracellular norepinephrine concentration. We collected samples using microdialysis from the rat basal forebrain, and measured the concentration of norepinephrine during baseline, saline, and acute ethanol administration using high performance liquid chromatography in the same animal. Using acute intravenous administration of ethanol (10%, 1 g/kg, 1 ml/min), we found an increase in norepinephrine of 74% above baseline immediately after infusion, in comparison to control. To rule out that the increase we measured was due to a stress response from the injection, we reduced the flow rate to 0.25ml/min and measured a norepinephrine increase of 100%, 20 minutes after infusion, compared to control. Saline infusion and 0.5 g/kg dose of 10% ethanol did not stimulate extracellular norepinephrine changes. The dialysate ethanol concentrations for both experiments peaked at 9 mM immediately after ethanol infusion. The peak occurred either immediately after the infusion with an infusion rate of 1 ml/min, or 10 minutes after ethanol infusion in the 0.25 ml/min experiment. In addition, histological analysis confirmed probe location spanning the basal forebrain from 2.4-0.00 mm anterior to bregma and included the nucleus accumbens shell, septum, and extended amygdala. All of these brain regions receive adrenergic projections from the brainstem. In conclusion, our data indicates a possible role of norepinephrine in the acute intoxication effect of ethanol in naïve rats which may be acting through the nucleus tractus solitarii projections to the basal forebrain, though this mechanism is unclear.

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Abstract 115

HYPERVALENT IODINE-MEDIATED SYNTHESIS OF 5/5, 5/6- SPIROIMINALS/SPIROAMINALS AND STUDYING THE EFFECT OF C25 SUBSTITUTION ON SPIROIMINAL/SPIROAMINAL FORMATION.

Naveen Kumar Rayala AYi Kou, and Seongmin Lee*

Affiliation: The Division of Chemical Biology and Medicinal Chemistry, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA.

Body of Abstract: Hypervalent iodine-mediated formation of spiroiminals and spiroaminals from steroidal amines are presented. A wide variety of natural compounds contain spiroaminal and spiroiminal moieties. For example, steroidal spiroaminals such as solasodine, solamargine, and tomatidenol have shown potent antitumor and anti-inflammatory activities. Here we are reporting the first example of hypervalent iodine-mediated formation of 5/5 spiroiminals. Under the influence of excess PhI(OAc)₂ and I₂ in acetonitrile, steroidal amines smoothly underwent cyclization to give 5/5 spiroiminals and 5/5 spiroaminals in a stereoselective manner. The formation of 5/5 spiroiminals presumably occurs through amine-to-imine oxidation followed by iminyl radical-mediated cyclization. Also we have observed unexpected formation of E-ring opened steroidal alkaloid from primary amine. Oxidative steroidal E-ring opening that occurs presumably via aminyl radical-mediated iodoamination followed by fragmentation of iodospiroaminal. The observation of formation of 5/6 spiroaminal and E-ring opened oxyimine from a primary and tertiary amines, respectively, has prompted us to further explore substrate-dependency of hypervalent iodine-mediated cyclization. Also, we are studying the effect of C25 substitution on spiroiminal/spiroaminal formation using this Hypervalent iodine-mediated synthesis.

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HALOPYRIDINES AS SWITCHABLE ELECTROPHILES: COVALENT DDAH INHIBITORS

Alfred Tuley Christopher Schardon, Sean Patel, Pamela Horton, Jake Swartzel, and Walter Fast

Body of Abstract: Human dimethylarginine dimethylaminohydrolase-1 (DDAH1) regulates nitric oxide signaling, and is a drug target for idiopathic pulmonary fibrosis, septic shock, and possibly melanoma progression. From a fragment-based screen, 4-halopyridines were identified as inhibitors of DDAH1 that use nucleophilic aromatic substitution to covalently modify the active-site Cys. Mechanistic studies revealed that the halopyridine remains largely unreactive as the neutral species in solution (a reactivity similar to acrylamides), but "switches on" to become 4500-fold more reactive when bound as the protonated pyridinium form (a reactivity similar to iodoacetamide). An active-site Asp stabilizes the pyridinium and this mechanism imparts significant selectivity to covalent modification. Using a fragment-linking approach to enhance non-covalent affinity for DDAH1, the halopyridine scaffold was derivatized using a homologous series of amino acid substituents. Kinetic parameters for inactivation (kinact, KI and kinact/KI) were used to determine the optimal linker length between the amino acid and halopyridine fragments, which revealed that a linker length of three atoms was optimal (kinact/KI of $51 \pm 27$ M$^{-1}$ s$^{-1}$), exhibiting a rate constant that is several orders of magnitude larger than the generic halopyridine scaffold. This study serves as an example for the application and optimization of "switchable electrophiles" as selective covalent enzyme inhibitors.

Funding: NIH grant R01 GM069754, Robert A. Welch 42 Foundation grant F-1572, NIH 1K12GM102745, NSF REU Summer Fellowship (CHE 1559839)

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Abstract 116
MEHP-INDUCED LEUKOCYTE INFILTRATION INTO THE TESTICULAR INTERSTITIUM OF PERIPUBERTAL RATS DOES NOT EXACERBATE MEHP-INDUCED GERM CELL APOPTOSIS

Jorine J.L.P. Voss, Angela R. Stermer, Rashin Ghaftari, Richa Tiwary, and John H. Richburg.
UT Austin College of Pharmacy, Division of Pharmacology and Toxicology

Body of Abstract: The testis is an immune-privileged organ that maintains an immune suppressive environment with few leukocytes in the testicular interstitium. We have previously shown that exposure of peripubertal (postnatal day (PND) 28) Fischer rats to an acute dose of MEHP, a well-described Sertoli cell toxicant, leads to an accumulation of CD11b+ cells in the interstitial space of the testis that closely correlates with a robust incidence of germ cell (GC) apoptosis. CD11b is expressed on the outer membrane of many leukocytes of the innate immune system, including monocytes, macrophages, and granulocytes. Here we test the hypothesis that the infiltrating immune cells contribute to germ cell death. PND 28 Fischer rats that received an oral dose of 700 mg/kg MEHP showed a significant CD11bc+ immune cell infiltrate consisting of both CD68+ cells, a monocyte and macrophage marker, and neutrophils, identified by morphology and the expression of myeloperoxidase. The numbers of both cell types peaked at 12 hours, but by 48 hours less than a quarter of the accumulated cells remained. Gene expression analysis of the testicular macrophages of MEHP-treated cells showed significantly upregulated expression of Tnfa and Il6, and the Arg1/Nos2 ratio was reduced compared to macrophages from the interstitium of control-treated testis, although small increases in Il10 and Tgfb1 were observed too. Depletion of circulating monocytes with clodronate liposomes prior to MEHP-treatment did reduce the macrophage influx into the testis, but did not lower germ cell apoptosis. Additionally, depletion of neutrophils using an anti-polymorphonuclear cells antibody prevented both macrophage and neutrophil infiltration into the testis, but also did not affect germ cell apoptosis. Together these results show that exposure to MEHP leads to a rapid and temporary influx of pro-inflammatory monocytes and neutrophils in the interstitium of the testis. However, with this dosing paradigm, they do not appear to exacerbate phthalate-induced injury to the testis and their functional significance remains unknown.

Funding: This work was funded, in part, by a grant from the National Institutes of Health/ National Institute of Environmental Health Sciences (NIH/NIEHS; 1R01 ES016591) and the Center for Molecular Carcinogenesis and Toxicology

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Fourteenth Annual Louis C. Littlefield Celebrating Pharmacy Research Excellence Day
In Professional, Graduate, and Postgraduate Programs

Abstract 117
SEX-DIFFERENCES IN GLUTAMATERGIC SYNAPTIC TRANSMISSION AND PLASTICITY IN NUCLEUS ACCUMBENS D1R+ MSNS OF DRD1A-TDTOMATO MICE DURING ADOLESCENCE

Heather C. Aziz  Richard A. Morrisett

Body of Abstract: The nucleus accumbens shell (NAc Sh), a component of the reward pathway in the brain, is thought to function as a mediator of action selection through dopaminergic reinforcement, encoded by glutamatergic inputs from the amygdala, ventral tegmental area, thalamus, hippocampus, and prefrontal cortex. Altered glutamatergic synaptic transmission and plasticity have been observed in NAc Sh medium spiny projection neurons (MSNs) following exposure to drugs of abuse. The NAc Sh is composed of a heterogeneous population of dopamine D1 receptor-expressing (D1R+) MSNs and non-D1R-expressing (D1R-) MSNs, functional in the direct and indirect pathways, respectively. Previous studies investigating sex-differences in the electrophysiological properties of NAc Sh MSNs are few in number and have provided conflicting results. The purpose of this study was to establish the electrophysiological properties of NAc Sh D1R+ MSNs in naïve male and female mice during mid-adolescence (post-natal days P35-P42). Sagittal brain slices from Drd1a-tdTomato mice were used for whole cell electrophysiological recordings. Recordings were conducted in D1R+ MSNs of the NAc Sh, identified via fluorescence microscopy. Vaginal samples were collected to establish the stage of estrous cycle in female mice.

Mid-adolescent, naïve, female NAc Sh D1R+ MSNs exhibited increased excitability and sEPSC frequency, but decreased glutamatergic plasticity. No observed sex-difference was seen in sEPSC amplitude. When cells from female mice were further split by stage of estrous cycle, no changes were seen in D1R+ MSN excitability, sEPSC frequency or amplitude. These results highlight previously undocumented sex-differences in glutamatergic synaptic transmission and plasticity of naïve D1R+ MSNs during mid-adolescence. Furthermore, the stage of the female estrous cycle does not appear to influence the parameters of glutamatergic synaptic transmission measured in this study.

We have established sex-differences in naïve NAc Sh D1R+ MSNs at a specific developmental stage. Future studies should consider sex and developmental stage of their animal model, as well as the naïve condition of the experimental target prior to beginning the study to aid in interpreting final results.

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EMERGENCY DEPARTMENT USE AND BARRIERS TO HEALTH CARE AMONG HOMELESS AND UNINSURED PATIENTS AT A STUDENT-RUN FREE CLINIC

Shayan Bhathena Dr. Leticia Moczygemba, Pharm.D., Ph.D.
Dr. Kenneth Lawson, Ph.D.
UT Austin College of Pharmacy, Division of Health Outcomes & Pharmacy Practice

Body of Abstract: Rationale: Free clinics often provide healthcare to homeless individuals who face barriers to accessing primary care and other healthcare services. This study aimed to:

1. Identify barriers to healthcare experienced by uninsured and homeless patients at a student-run free clinic.
2. Assess patient perceptions of helpfulness of social service resources.
3. Examine the relationship between barriers and emergency department (ED) use and health status.

Methods: In 2017, patient interviews were conducted at a student-run free clinic in central Texas. A questionnaire was used to collect demographics, health status, ED usage, and ratings of barriers to health care and helpfulness of social service resources. Data analyses included descriptive and bivariate analyses (Chi-squared and Kruskal-Wallis tests). The UT IRB approved this study.

Results: A total of 48 patients participated. The highest reported patient barrier was cost of healthcare, followed by lack of transportation and lack of insurance. Resources with the highest patient usage were shelters or transitional living facilities, followed by caseworkers and the Medical Access Program (MAP). Of the top 5 most utilized resources, Medicaid was rated as most helpful, followed by MAP and caseworkers. There was a significant relationship between lack of transportation and ED use (p=0.03), use of a local mental health services program and ED use (p=0.01), and type of insurance and ED use (p=0.01). Of these, groups with the greatest proportions of participants who reported one or more ED visits in the past 6 months were those who rated lack of transportation as a moderate barrier, those who currently use the local mental health services program, and those covered by Medicare or Medicaid. No significant relationship was found between any health care barriers and health status.

Conclusion: The results of this study can be used to help design and implement interventions and resources that more effectively facilitate healthcare access for this free clinic’s patient base. For example, lack of transportation was related to ED use, so the free clinic might consider administering free bus passes to patients who need transport for medical appointments.

Funding: n/a
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Abstract 119
TRIPLEX-FORMING OLIGONUCLEOTIDES POTENTIATE THE ANTI-TUMOR ACTIVITY OF GEMCITABINE AGAINST HUMAN TUMORS IN MICE

Laura A. Christensen  Stephen B. Boulware, UT Austin College of Pharmacy, Division of Pharmacology and Toxicology
Zhengrong Cui, UT Austin College of Pharmacy, Division of Pharmaceutics
Rick A. Finch, UT MD Anderson Cancer Center, Department of Veterinary Sciences
Karen M. Vasquez, UT Austin College of Pharmacy, Division of Pharmacology and Toxicology

Body of Abstract: Rationale: The anti-cancer drug gemcitabine (GEM) is a pyrimidine analog that inhibits DNA synthesis and induces apoptosis. Triplex-forming oligonucleotides (TFOs) are single-stranded oligonucleotides that can bind site-specifically to duplex DNA to form a triple helix. We hypothesized that the effectiveness of GEM could be improved if administered in combination with TFOs targeting oncogenes that are amplified in human tumors (e.g., c-MYC). TFOs can direct DNA damage and induce unscheduled DNA repair synthesis (UDS) at the target site, potentially triggering the incorporation of GEM and improving its efficacy.

Methods/Results: TFO binding to genomic DNA in human cancer cells with amplified c-MYC was verified by gel shift assay. TFO-induced DNA damage was confirmed via a chromatin immunoprecipitation assay using an antibody against NBS1, a marker for DNA double-strand breaks. To determine if TFO-induced DNA damage would increase GEM incorporation, cells were treated with TFO and [3H]GEM. An ~10-fold higher incorporation of [3H]GEM into DNA was seen with TFO+GEM versus GEM only. Human tumors containing amplification of c-MYC were implanted into athymic mice, and a c-MYC-targeted TFO was administered in combination with GEM. Tumor volumes were measured at regular intervals to evaluate tumor growth delay. Treatment with TFO+GEM resulted in significantly greater tumor growth delay than GEM or TFO alone.

Conclusion: TFOs were used to direct site-specific damage to the human c-MYC oncogene, inducing UDS and triggering the incorporation of GEM. TFO+GEM treatment significantly delayed tumor growth in mice bearing human tumor xenografts. Combining antimetabolite chemotherapies with triplex technology may improve the anti-tumor activity of traditional chemotherapeutic agents and reduce host toxicity. To improve the delivery of TFOs to tumor cells, initial experiments have been performed to develop a nanoparticle-based TFO delivery system. Preliminary results indicate that this delivery system can enhance the delivery of a c-MYC-specific TFO to HER2-over-expressing tumor cells. Future studies include developing TFO nanoparticles to target oncogene-specific TFOs selectively to tumors in vivo and studying the efficacy of using TFO nanoparticles in combination with a GEM nanoparticle formulation.

Funding: National Institutes of Health (to K.M.V.); Grant numbers: CA097175; CA093729; Grant sponsor: University Cancer National Institutes of Health (to K.M.V.); Grant numbers: CA097175; CA093729; Grant sponsor: University Cancer NIH Grant numbers CA097175 and CA093279; University Cancer Fund at UT MD Anderson Cancer Center

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Abstract 121

DEVELOPMENT OF A DUAL-REPORTER, FLUORESCENCE-BASED ASSAY FOR MODULATORS OF GENETIC INSTABILITY

Imee M. A. del Mundo, Eun Jeong Cho, Kevin N. Dalby, *Karen M. Vasquez
1Division of Pharmacology and Toxicology, College of Pharmacy, Dell Pediatric Research Institute, UT Austin
2Division of Chemical Biology and Medicinal Chemistry, College of Pharmacy, UT Austin

Body of Abstract: Mutation “hotspots” in the genome often co-localize with DNA sequences that can adopt alternative DNA structures (i.e., non-B DNA, such as H-DNA). Non-B DNA-forming sequences are recognized as an endogenous source of genetic instability, a hallmark of many genetic diseases, including cancer. However, mechanisms of non-B DNA-induced genetic instability are still unclear. To this end, we will use small molecules to modulate DNA structure to study the mutagenic outcome. We hypothesize that genetic instability associated with non-B DNA correlates with the stability of the structure. To test this hypothesis, we developed an assay to detect triplex/H-DNA-destabilizing or –stabilizing ligands.

Our goal was to develop a sensitive and efficient high throughput screen (HTS)-based assay. Three fluorescence-based assays were considered: 1) an intermolecular triplex with a fluorophore-quencher combination; 2) an intramolecular triplex amenable for a fluorescent intercalator displacement (FID) assay; and 3) an intramolecular triplex with a fluorophore-quencher combination.

Our investigation has led us to select the intramolecular triplex system (R2-FQ), labeled with the FAM-BHQ1 fluorophore-quencher pair, positioned such that when the triplex is intramolecularly folded, BHQ1 partially quenches the FAM fluorescence. This dual-reporter system affords detection of both triplex-stabilizing and triplex-destabilizing ligands.

In the presence of known triplex-stabilizing ligands (e.g. intercalators, BePI or coralyne), the FAM signal decreased. In the absence of available triplex-destabilizing ligands, we used a DNA sequence that is complementary to the Hoogsteen H-bonding strand (‘3rd strand’), MCRa2. Its binding to the 3rd strand facilitated the separation of the FAM from BHQ1, leading to increased FAM emission. We were also able to identify a buffer condition with an optimal signal-to-noise ratio which supports weak folding of the triplex (20 mM Tris buffer pH 7.4, 0.01% Tween, +/- 10 mM Mg2+). In a preliminary HTS screen using this assay, we identified both potential triplex stabilizers and destabilizers.

Funding: NIH/NCI CA093729 to KMV

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REAL TIME FLUORESCENCE-BASED BIOCHEMICAL SCREENING ASSAY FOR IDENTIFICATION OF INHIBITORS TARGETING HUMAN DNA POLYMERASE θ (POLQ)

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Body of Abstract: In mammalian cells, POLQ (pol θ) is an unusual specialized DNA polymerase that plays a major role in defending cells against agents, including X-rays, which cause DNA strand breaks. Recent work shows the mechanism of suppression of chromosomal instability by POLQ through a pathway of alternative DNA end-joining, and the biological relevance of this pathway to survival of cancer cells, which makes POLQ an important therapeutic target to cure breast cancer cells and increase sensitivity to IR. In this research, we aimed to identify an antagonist that can reduce POLQ activity utilizing high throughput compound screening.

We hypothesize a simple, homogeneous and cost-effective assay, that is robust and amenable to high throughput screen, can be developed for identifying specific POLQ inhibitors. A real-time fluorescence assay was established for high throughput small molecule inhibitor screening. An active recombinant fragment of POLQ was used to catalyze DNA synthesis and strand displacement with a reporter–quencher substrate. In the presence of inhibitor, the reduction of polymerase activity inhibits the displacement of reporter–quencher substrate, resulting decrease of fluorescence intensity. Due to the inconsistent lag time, the assay was monitored kinetically and the both rate and end-point fluorescence was recorded. The assay was then optimized for buffers, incubation time, additives, and other factors on both 96 and 384 well formats. The assay tolerance to DMSO and room temperature were also investigated. The assay validation resulted z’ over 0.8 in a 96well format, demonstrating its suitability for high throughput compound screening. POLQ was screened in parallel with RB69 gp43 DNA polymerase as a specificity control. Over 1,700 small molecules of commercially available nucleotide analogs, FDA approved drug library, and kinase inhibitors with known activities were screened as a pilot screen. Although no strong inhibitors were identified, a few compounds have demonstrated moderate reduction of polymerization activities of POLQ. Two compounds were selected as lead candidates and are being further evaluated.

Funding: Cancer Prevention and Research Institute of Texas (CPRIT) grant RP160657.

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Abstract 123

DEFICIENCY IN THE MANGANESE EFFLUX TRANSPORTER SLC30A10 INDUCES SEVERE HYPOTHYROIDISM IN MICE.

Steven Hutchens Chunyi Liu, UT Austin; Thomas Jursa, UC Santa Cruz; William Shawlot, UT Austin; Beth Chaffee, MD Anderson; Weiling Yin, UT Austin; Andrea Gore, UT Austin; Michael Aschner, Albert Einstein College of Medicine; Donald Smith, UC Santa Cruz; Somshuvra Mukhopadhyay, UT Austin.

Body of Abstract: Manganese is an essential metal that becomes toxic at elevated levels. Loss-of-function mutations in SLC30A10, a cell-surface-localized manganese efflux transporter, cause a heritable manganese metabolism disorder resulting in elevated manganese levels and parkinsonian-like movement deficits. The underlying disease mechanisms are unclear; therefore, treatment is challenging. To understand the consequences of loss of SLC30A10 function at the organism level, we generated Slc30a10 knock-out mice. During early development, knock-outs were indistinguishable from controls. Surprisingly, however, after weaning and compared with controls, knock-out mice failed to gain weight, were smaller, and died prematurely (by ~6-8 weeks of age). At 6 weeks, manganese levels in the brain, blood, and liver of the knock-outs were ~20-60-fold higher than controls. Unexpectedly, histological analyses revealed that the brain and liver of the knock-outs were largely unaffected, but their thyroid exhibited extensive alterations. Since hypothyroidism leads to growth defects and premature death in mice, we assayed for changes in thyroid and pituitary hormones. At 6 weeks and compared with controls, the knock-outs had reduced thyroxine levels (~50-80%) and increased thyroid-stimulating hormone levels (~800-1000-fold), indicating that Slc30a10 knock-out mice develop hypothyroidism. Importantly, a low-manganese diet produced lower tissue manganese levels in the knock-outs and rescued the phenotype, suggesting that manganese toxicity was the underlying cause. Our unanticipated discovery highlights the importance of determining the role of thyroid dysfunction in the onset and progression of manganese-induced disease and identifies Slc30a10 knock-out mice as a new model for studying thyroid biology.

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ANAPLASTIC LYMPHOMA KINASE, A RECENTLY-DISCOVERED REGULATOR OF RESPONSES TO ETHANOL, HAS CIRCUIT- AND SEX-SPECIFIC INFLUENCES ON VTA GABA TRANSMISSION

Regina A. Mangieri, Heather C. Aziz, Richard A. Morrisett
UT Austin College of Pharmacy, Division of Pharmacology and Toxicology

Body of Abstract: Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase implicated in biochemical, physiological, and behavioral responses to ethanol by flies, rodents, and humans. Moreover, ALK inhibitors reduce ethanol consumption in mouse models, suggesting ALK is a promising target for the treatment of alcohol use disorder. Work by our lab and others suggests that one mechanism by which ALK manipulations could impact drinking is by regulating inhibitory transmission in the ventral tegmental area (VTA). We tested this hypothesis by examining the effects of an ALK inhibitor, alectinib, on GABAergic inhibitory postsynaptic currents (IPSCs) in acutely prepared, adult, male and female mouse brain slices, under baseline conditions and during in vitro ethanol treatment. When we segregated the data collected from VTA dopamine (DA) neurons based on an electrophysiological parameter classically used to define DA neurons, we found that alectinib (100 nM) differentially altered IPSC frequency in subpopulations of neurons. As VTA DA neurons of different brain circuits (e.g., mesocortical vs. mesolimbic) vary in this electrophysiological parameter, these results imply that the effects of ALK inhibition on baseline inhibitory transmission are not the same across all dopaminergic circuits. We then tested whether alectinib blocked the effects of ethanol on IPSCs in VTA DA neurons. Alectinib (100 nM) attenuated 50 mM ethanol-induced potentiation of IPSC amplitudes, but did not exert a strong effect on ethanol enhancement of IPSC frequency, with trends for treatment X sex interactions for both measures. Results from male mice revealed no significant effects of alectinib treatment on ethanol potentiation of IPSCs, whereas in females there was a significant attenuation of ethanol-potentiated IPSC amplitudes by alectinib and a tendency toward reduction of ethanol-potentiated IPSC frequency. Thus, alectinib may be more efficacious in reducing the effects of ethanol on inhibitory transmission in the VTA of female versus male mice. In sum, this work shows that ALK inhibition exerts complex effects on inhibitory transmission in the VTA and future studies will further examine interactions between sex and circuitry in the attenuation of ethanol-enhanced GABA transmission in the VTA by alectinib.

Funding: This work was supported by the National Institute on Alcohol Abuse and Alcoholism Integrative Neuroscience Initiative on Alcoholism award AA016651.

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PROTEOMICS FACILITY

Maria Person Michelle Gadush
Division of Pharmacology and Toxicology

Body of Abstract: The Proteomics Facility uses high resolution, high sensitivity Orbitrap Fusion mass spectrometers to provide protein identification and quantitation services and conduct post-translational analysis of protein phosphorylation, acetylation, methylation and ubiquitinylation. We collaborate in studies on unusual modifications, crosslinking, and isotope label based quantitative proteomics.

Funding: None

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MONO-(2-ETHYLHEXYL) PHTHALATE (MEHP) REVERSIBLY DISRUPTS BLOOD TESTIS BARRIER (BTB) IN PRE-PUBERTAL RATS

Richa Tiwary  Rashin Ghaffari, Jorine Voss and John H. Richburg  
Center for Molecular and Cellular Toxicology, College of Pharmacy, The University of Texas at Austin

**Body of Abstract:** The blood testis barrier (BTB) constitutes an unique microenvironment for developing spermatocytes, is a well-studied target of numerous environmental toxicants. MEHP is the active metabolite of a widely used plasticizer (DEHP) in commercial products and has been recognized as a reproductive toxicant. Here, the influence of MEHP on BTB integrity is described as well as the signal transduction pathways that underlie this effect. Treatment of Post Natal Day (PND) 27 rats with 700 mg/kg MEHP for 24 hours perturbed the BTB integrity as indicated by a biotin tracer assay. Additionally, MEHP treatment induced transient surge of p44/42 Mitogen Activated Protein Kinase (MAPK)- JNK1/2, p38 and ERK protein levels; possibly instigated via the observed enhanced expression levels of pro-inflammatory cytokines-IL-6 and TNF as indicated by qPCR analysis. Concomitant with decreased expression and mislocalization of ZO1 and occludin, sloughing of germ cells were observed in MEHP treated pre-pubertal rats. We further investigated that MEHP treatment of PND 27 rats with 700 mg/kg MEHP followed by a recovery period of 5 weeks could reverse the BTB disruption. Taken together, these findings indicate a role for the MAPK pathway in instigating the disruption of the BTB disruption after MEHP exposure; although this effect on the BTB was reversible.

**Funding:** (NIH/NIEHS; 1R01 ES016591)

Environmental Health Sciences (NIH/NIEHS; 1R01 ES016591)

Class of Presentor: Staff Scientist  
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A HIGH-THROUGHPUT SCREENING PLATFORM FOR MONITORING GTPASE ACTIVITY OF FEOB (FERROUS IRON TRANSPORT PROTEIN B)

John Veloria, UT Austin College of Pharmacy, Targeted Therapeutic Drug Discovery and Development Program
Ashwini Devkota, UTCOP, Targeted Therapeutic Drug Discovery and Development Program
Eun Jeong Cho, UTCOP, Targeted Therapeutic Drug Discovery and Development Program
Minhye Shin, Shelley Payne UT Austin College of Natural Science, Molecular Biosciences
Kevin Dalby, UTCOP, Targeted Therapeutic Drug Discovery and Development Program and Division of Chemical Biology and Medicinal Chemistry

Body of Abstract: Introduction: FeoB is a transmembrane protein that acts as an iron transporter in prokaryotes, where it has been implicated in virulence for several pathogenic bacteria. It contains a C-terminal transmembrane anchor and an N-terminal domain that closely mimics eukaryotic G-proteins. However, the GTPase activity of FeoB is not well understood, and currently, there are no reported inhibitors. Thus, we sought to develop platforms that are capable of identifying new inhibitors of the GTPase activity of FeoB.

Rationale: We first wanted to develop a robust biochemical assay that can be adaptable for high throughput inhibitor screening of novel GTPase inhibitors, and validate primary hits orthogonally using a luminescence detection system. We hypothesized that a colorimetric detection system can be produced to screen for novel inhibitors in a 384-well format, improving over traditional assay methods. The rationale behind this research is that we can successfully develop, optimize, validate, and implement a high throughput screening format that can be used to screen for novel inhibitors of FeoB in a cost-effective manner.

Method: First, we examined the interaction between the N-terminal domain of FeoB (NFeoB) and GTP to develop a colorimetric assay that utilizes malachite green to detect phosphate generation. Next, we optimized the assay to ensure compatibility in microplates, while focusing on the creation of a stable assay that uses low enzyme concentrations and tolerates assay additives such as DMSO and detergents. Next, we utilized a luciferase-coupled reaction to further examine NFeoB GTPase activity using luminescence-based detection system.

Results: The assays proved to be stable, robust, and suitable for high-throughput screening. The modified colorimetric-based detection system demonstrated its potential to identify new small molecule inhibitors. Additionally, a luminescence-based platform was capable of being utilized to confirm new inhibitors that were identified in the initial colorimetric screen.

Conclusion: We have successfully developed a new screening platform targeting FeoB GTPase activity, utilizing both colorimetric and luminescence-based detection systems. Together, these may act a simple and cost-effective way to identify new GTPase inhibitors in a high-throughput manner.

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MECHANISMS OF DNA STRUCTURE-INDUCED TRANSLOCATION BREAKPOINT HOTSPOTS IN HUMAN CANCER GENOMES

Junhua Zhao, Guliang Wang, Imee M. del Mundo, Jennifer A. McKinney, Xiuli Lu, Albino Bacolla, Stephen B. Boulware, Changsheng Chang, Haihua Zhang, Pengyu Ren, Catherine H. Freudreich, and Karen M. Vasquez*

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Body of Abstract: Regions of the genome that are susceptible to chromosome alterations, or “hotspots”, are often mutated in human cancer, yet the mechanisms involved in the generation of these cancer-associated mutations are largely unknown. Repetitive DNA sequences capable of adopting alternative DNA structures often co-localize with chromosomal breakage/mutation hotspots1-3. Previously, we found that an H-DNA-forming sequence from the c-MYC gene that maps to a translocation hotspot in human diseases such as lymphoma, leukemia, and plasmacytoma4-6, stimulates DNA double strand breaks (DSBs), deletions, and translocations in mammalian cells and mice7,8. However, the mechanism(s) of H-DNA-induced genetic instability is largely unknown. Here, we report that alternative DNA structure-forming sequences (i.e. H-DNA) are enriched at (within 100-bp upstream or downstream to) translocation breakpoint hotspots in human cancer, implicating DNA structure in human cancer etiology. Further, we found that H-DNA-induced genetic instability was suppressed in human cells deficient in the nucleotide-excision repair nucleases, ERCC1-XPF and XPG, but stimulated in the absence of FEN1, a replication-related endonuclease, implicating DNA repair and replication nucleases in processing mutagenic DNA structures. We also identified novel mechanisms of genetic instability triggered by H-DNA through distinct structure-specific, cleavage-based replication-independent and replication-dependent mechanisms. Thus, these results reveal a new paradigm of DNA structure-induced genetic instability in human disease, and provide critical information on the role of DNA structure in the etiology of cancer.

Funding: This work was supported by an NIH/NCI grant to K.M.V. (CA093729).

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NEGATIVE AFFECT-ASSOCIATED USV ACOUSTIC CHARACTERISTICS PREDICT FUTURE EXCESSIVE ALCOHOL DRINKING AND ALCOHOL AVOIDANCE IN P AND NP MALE RATS

Duvauchelle Laboratory University of Texas College of Pharmacy, Pharmacology and Toxicology Division

Body of Abstract: Negative emotional status plays an important role in alcohol use disorders, such that individuals experiencing greater levels of adverse emotional events are more vulnerable to developing alcohol use disorders (AUDs). Indeed, negative life events (e.g., abuse, trauma, discrimination) contribute to negative emotional status and to the risk of developing AUDs. Ultrasonic vocalizations (USVs) emitted by rats serves as a well-established model of emotional status that can reflect positive and/or negative affective responses in real-time. When applied to rats selectively bred for high- and low-alcohol consumption, USVs can provide an emotional phenotype of alcohol vulnerable and alcohol-resistant individuals. Though most USV studies are limited to assessing only USV counts, each individual USV is a multi-dimensional data point consisting of several acoustic characteristics with the potential to provide further insight into the neurocircuitry underlying emotional response. To determine whether acoustic characteristics can be used to differentiate between rats selectively bred for high- and low-alcohol consumption, we recorded USVs emitted from alcohol-naïve and alcohol-experienced P and NP rats and utilized advanced statistical analyses (linear mixed models-LMM and linear discriminant analyses-LDA) to analyze USV acoustic characteristics (e.g., frequency in kHz, USV duration, power and bandwidth) of negative (22-28 kHz) and positive (50-55 kHz) affect-related USVs between rat lines (e.g., high versus low drinkers). Using these analyses, we were able to develop a model to determine rat line membership purely on the acoustic characteristics of their 22-28 kHz USV emissions. In other words, with the use of advanced statistical techniques and negative USV emissions, we can confidently identify the future drinking levels of individual animals most likely to be vulnerable to excessive alcohol drinking and those most resistant to alcohol abuse. The differences in USV characteristics may indicate differences in affect-related motivation to consume alcohol and associated neural pathways mediating emotional response. Characterizing these differences would allow for the targeting of dysregulated emotional states seen in human alcohol abusers.

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Abstract 130

ATOVAQUONE AMORPHOUS SOLID DISPERSIONS IMPROVED BY COMBINING SPONTANEOUS EMULSIFYING COMPONENT AND HOT MELT EXTRUSION

Hiroyuki Takabe Daniel Alan Davis, Zachary N. Warnken and Robert O. Williams III
UT Austin College of Pharmacy, Molecular Pharmaceutics and Drug Delivery

Body of Abstract: Purpose

Formulating insoluble drugs using amorphous solid dispersions (ASDs) is limited by low drug loading, low drug dissolution and rapid precipitation due to supersaturation. We aim to broaden the extrusion window for lowering extrusion temperatures and enhancing dissolution of high-dose atovaquone (solubility 0.2 µg/mL), by combining spontaneous emulsifying component (SEC) and hot melt extrusion (HME).

Methods

Type and ratio of SEC excipients to maximize solubility of atovaquone. Benzyl benzoate, Tween 20 and Polyethylene glycol 400 were chosen as the oil, surfactant and cosurfactant, respectively. Various ratios were studied to determine the highest solubility of atovaquone (10 mg/mL) while still maintaining solubility with the HME polymer and spontaneous emulsifying capacity upon dilution. Affinisol, Kollidon VA64 and polyvinylpyrrolidone K30 (PVP) were studied using Flory-Huggins modeling for selecting polymer. HME was conducted as follows: 10 g was manually fed into the extruder with a screw speed of 150 RPM and barrel temperature at 180°C. Dissolution testing was conducted as follows: Extrudate was milled to form particles that passed through a 600 µm screen; compressed into 300 mg tablet; and tested in a USP II apparatus, 900 mL of deionized water at 37°C and paddle speed of 75 RPM.

Results

SEC and HME increased dissolution of atovaquone in an ASD. Screening studies confirmed drug-polymer compatibility. Flory-Huggins modeling predicted that PVP K30 had the highest miscibility with atovaquone and was selected for further study. Tablet dispersibility showed that the compressed tablet containing SEC rapidly wetted and dispersed in water, whereas the control tablet did not wet or disperse well in water.

Conclusion

Combining SEC and HME processing to formulate a high dose, poorly water-soluble drug like atovaquone increased both the processing window for extrusion as well as the dissolution of atovaquone solid amorphous dispersions.

Funding:

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