AACP REPORT

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Feasibility of a Concierge Pharmacy Service Incorporating Pharmacogenomics

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Objective: To survey potential users and pilot a 24/7 concierge pharmacy service within a private practice and quantify the number of clinically actionable examples of pharmacogenomics in an ambulatory care population. Methods: Eligible subjects included those 18+ years old and patients of supporting physicians at the clinic. After consenting, subjects completed a survey regarding pharmacy services and willingness to pay. Pharmacogenomic testing (n=34) included collecting DNA from buccal swabs and genotyping by RT-PCR. A subset of participants (n=6) piloted a free 24/7 concierge pharmacy service for one month. Results: Pre-survey findings highlighted that the majority of subjects would utilize an in-person pharmacist service to review medications ~4 times a year (mean score = 8.6 out of 10). The average score dropped to 4.6/10 if insurance did not cover costs. Use of an on-call pharmacy service as well as if insurance covered 50% of total costs averaged 5/10. Nonetheless, 23 subjects (67%) indicated willingness to pay $25-$50 per month for individual pharmacy services, although 6 subjects (18%) would not pay anything out of pocket. In the concierge service, two subjects (33%) utilized the on-call pharmacist. Preliminary pharmacogenomic results identified a range of 6-34% of subjects who have the potential for clinical changes based on ultra-rapid or poor metabolism. Implications: Subjects prefer to sit down with a pharmacist for medication services, and the primary barrier is likely cost. Commercial pharmacogenomic testing is currently underway for the pilot, and these results will be reported in charts and used for clinical decision-making as warranted.

Development of a Clinical Decision Algorithm for Adults Hospitalized with Pneumonia

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Objective: In patients with CAP, 1) determine the accuracy of published MRSA PMs, and 2) identify a PM that maximizes accuracy for MRSA. Methods: Records of patients with CAP (1/2014-3/2018) from an academic medical center (NMH) and a community teaching hospital (LFH) were searched. Positive blood or respiratory cultures defined MRSA CAP. Classification matrices compared PM performance. Predictive accuracy (50-100%), and accuracy adjusted to remove the effect of chance [ie, Effect Strength for Sensitivity (ESS) = 0 (chance) - 100% (perfect classification), were quantified for each PM. De novo PMs were developed using ODA for R. Results: 1231 patients (73% NMH, 50% males, 27% ICU, 64% PORT IV-V) were included. MRSA CAP (1.7%) and nasal colonization (5.7%) were uncommon. Thirty-day mortality and readmission were 4.1% and 16.5%, respectively. Low-sensitivity (33%, 24%, 43%), moderate/high-specificity (79%, 91%, 80%), and weak ESS (12.3, 14.9, 22.5) characterized three published PMs. Structural decomposition of the sample using ODA identified a two-step PM. Step one: if age ≤ 70.5, predict MRSA (2.7%), otherwise predict no MRSA (99.5%) [sensitivity, specificity, ESS: 85.7%, 45.6%, 31.3]; step two: if PORT V, predict MRSA (2.6%), otherwise predict no MRSA (100%) [sensitivity, specificity, ESS: 100%, 80.5%, 80.5]. Implications: Despite the low prevalence of MRSA (1.7%), literature-based PMs had low sensitivity. While alternative PMs increased sensitivity (rule-out), these models would lead to routine overtreatment of MRSA in CAP; however, they can assist diagnostic-stewardship.

Long-Term Retention of ACLS Knowledge After AHA ACLS Certification

Susan E. Smith, University of Georgia College of Pharmacy, Kelly C. Rogers, University of Tennessee College of Pharmacy, Andrea Sikora Newsome, University of Georgia College of Pharmacy, Michael Fulford, University of Georgia College of Pharmacy.
Objective: Evaluate the impact of American Heart Association (AHA) certification in advanced cardiovascular life support (ACLS) on long-term retention of ACLS confidence and knowledge in PharmD students. Methods: A cross-sectional survey assessing demographics and ACLS confidence and knowledge retention was distributed to students at least one year following ACLS education at two colleges of pharmacy, both of which require didactic education on ACLS and offer an elective course that culminates in AHA certification. Respondents were grouped based on whether they received didactic education alone (no certification) or completed an elective course (AHA certification). The primary outcome was a score on the knowledge assessment of ≥80%. Secondary outcomes included confidence as assessed by the Dreyfus model. Binary logistic regression was applied to the primary outcome to account for potential confounding variables. The Chi-squared and Mann-Whitney U tests were performed in SPSS to compare categorical and continuous variables, respectively. Results: The survey was completed by 174 participants, 135 without and 39 with AHA certification. Students receiving AHA certification were almost three times more likely to score ≥80% on the knowledge assessment (41% vs. 15%; \( p < .001 \)). The association between AHA certification and knowledge retention remained after adjusting for potentially confounding variables (OR, 3.566; 95% CI, 1.467-8.667). Confidence was higher in the AHA certification group for 11 of the 15 questions assessed (\( p < .05 \)). Implications: AHA certification, compared to didactic teaching alone, resulted in increased long-term retention of ACLS knowledge and confidence. Consideration should be given to expansion of AHA certification in the PharmD curriculum.

MicroRNA Evasion as a Mechanism for Multidrug Resistance in Ovarian Cancer

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Objectives: The objectives of this research were to develop novel tools to detect drug transporter mRNAs as well as to molecularly target drug transporters to sensitize HGSOC to chemotherapy. Methods: High-grade serous ovarian cancer (HGSOC) is the most aggressive ovarian cancer subtype and is often diagnosed at an advanced stage. The standard of care still remains combination chemotherapy, but most patients develop drug resistant disease. Although chemoresistance involves increased expression of drug transporters, there is controversy over the actual mRNA levels detected in tumors. This may be due to shortening of the mRNA through alternative polyadenylation which evade current detection tools. Truncated mRNAs can also evade normal regulation by miRNAs. We developed primers and used different types of PCR to detect drug transporter mRNAs of different lengths. Western blot analysis was used to verify protein expression. Cell viability assays were used to detect changes in cell survival after treatment of cisplatin drug resistant cells with drugs and/or anti-sense oligonucleotides (ASO). Results: We were able to reliably detect mRNAs of drug transporters ABCC1 and ABCB1. The mRNA of ABCC1 was truncated in one HGSOC cell line. Knockdown of ABCC1 using siRNAs as well as a novel ASO we developed resulted in significant reduction in cell survival in cisplatin drug resistant HGSOC cells. Implications: The PCR primers we developed can potentially be used to reliably detect levels of drug transporters in the clinical setting. Targeting drug transporter mRNA at the molecular level using ASO can sensitize drug resistant tumors to chemotherapy.

Increasing Naloxone Access in Independent, Community Pharmacies

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Objective: The purpose of this study was to identify barriers to and facilitators of naloxone dispensing in independent, community pharmacies in Georgia. Methods: A semi-structured interview guide was used to assess pharmacists’ knowledge, attitudes, and beliefs regarding naloxone training, continuing education regarding naloxone and its policies, motivators and barriers to keep naloxone in stock, pricing models, naloxone patient education, and substance use disorder and opioid use. Seven in-depth, key informant interviews were conducted with community pharmacists. Data were content analyzed using the constant comparison method and a modified grounded theory approach. Emergent themes were categorized into barriers and facilitators. Results: Primary facilitators included: (1) awareness of Georgia’s standing order, (2) self-guided education and information-seeking efforts regarding naloxone, (3) positive attitudes toward patient counseling for naloxone use, and (4) perceived openness to use naloxone. Barriers included: (1) lack of detailed understanding of Georgia’s standing order, (2) stigma among community members regarding opioid abuse and misuse, (3) perceived reluctance of some/rural community members to discuss naloxone counseling, and (4) incentives to stock naloxone. Implications: Findings support pharmacists’ general awareness of and interest in Georgia’s standing order to dispense naloxone but may benefit from additional detailed education and training specific to Georgia’s standing order for...
naloxone dispensing, as well as communication support, particularly in rural communities where perceived sigma is a significant barrier.

**Sphingolipid Metabolism as a Marker of Hepatotoxicity in Drug-Induced Liver Injury**

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**Objective:** To structurally define and quantitatively measure individual sphingolipids from human primary hepatocytes exposed to acetaminophen. **Methods:** Here, we present an analytical platform that provides multidimensional mass spectrometry-based datasets for comprehensive structure characterization of sphingolipids extracted from human primary hepatocytes (HPH) exposed to toxic levels of acetaminophen (APAP). The hepatocytes were treated with APAP at 5 mM, 10 mM, and 20 mM over 24 hours. Sphingolipid extraction from hepatocytes involved a liquid/liquid extraction procedure that included a base hydrolysis step. The extracted HPH sphingolipids were analyzed using a combination of C18 reverse-phase chromatography, traveling wave ion mobility, and high-resolution data independent tandem mass spectrometry. **Results:** Our analytical approach generated mass spectrometry-based multidimensional data for comprehensive structure and abundance analysis of sphingolipids extracted from hepatocytes. Sphingolipid metabolism was responsive to hepatotoxicity as defined by specific sphingolipid structures being differentially expressed when exposed to toxic levels of APAP. Sphingolipid metabolism was not only broadly perturbed by APAP toxicity but was specifically and dose dependently responsive to varying levels of APAP exposure indicating sphingolipid metabolism is a key biological network intimately involved in hepatocyte toxicity. **Conclusions:** Sphingolipid structure analysis highlighted the important role individual sphingolipids play in response to hepatotoxicity. Our data lays the foundation for further investigation into how sphingolipid metabolism can provide new mechanistic insight into the role of hepatotoxicity and potential for reducing the cost and time burden of drug development by being applicable to not only APAP-induced toxicity but drug toxicity in general.

**Design and Development of Novel NDM-1 β-Lactamase Inhibitors to Combat Multidrug Resistant Bacteria (Superbugs)**

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**Objective:** To design and develop novel New Delhi metallo-β-lactamase-1 (NDM-1) inhibitors and restore the activity of antibiotics towards treating antibiotic-resistant (superbug) infections. **Methods:** Virtual screening was conducted utilizing Schrodinger software to generate pharmacophores with best binding interactions. We developed a focused library of unnatural alpha amino acids, boronic acids and lactams with best docking scores. A series of unnatural alpha amino acids were synthesized by boron-mannich multicomponent reaction (Petasis reaction). The unnatural alpha amino acids were obtained by reacting the aldehyde, amine and boronic acid in one-pot under mild conditions to obtain the amino acid. Boronic acids and lactams were obtained from commercial sources. We investigated in vitro inhibitory activity of synthesized compounds against NDM-1 expression strains of *E. coli* and *K. pneumoniae*. **Results:** We designed novel alpha amino acid pharmacophores with best binding interactions in the enzyme pocket. We employed a green-chemistry approach to synthesize the alpha amino acids in one step from mild environmentally benign boronic acid substrates. Whenever possible commercially available boronic acids and lactams were obtained. We identified few compounds with in vitro activity against NDM-1 expressing strains. **Conclusions:** In summary, a series of unnatural alpha amino acids were designed and synthesized utilizing an efficient approach and established there in vitro efficacy against NDM-1 producing strains.