AACP REPORT

New Investigator Award Recipients Poster Abstracts Presented at the 123rd Annual Meeting of the American Association of Colleges of Pharmacy, July 23-27, 2022

Development of a Transdermal System of Naloxone for Treatment of Opioid Overdose

Dorcas A. Frempong, East Tennessee State University, Akeemat O. Tijani, East Tennessee State University, Ashana Puri, East Tennessee State University, Prashant Dogra, Houston Methodist Research Institute, Dhruv Mishra, Northern Arizona University, Amruta Dandekar, Mercer University, Ajay Banga, Mercer University. Objective: Naloxone (NAL), an FDA approved drug is used in the treatment of opioid overdose. It is currently delivered as an IV, IM, SC injection, and intranasal spray. These routes may require multiple dosing due to short half-life of NAL that can be eliminated by developing a transdermal system that provides rapid onset and sustained drug delivery. Our study aimed to develop a skin patch for delivering NAL as an alternative option for opioid overdose treatment. Methods: The feasibility of using Microneedles (MNs) and ablative laser for transdermal delivery of NAL was determined. Porcine skin was treated with solid MNs and laser, respectively to assess their effect on NAL delivery in vitro. The lag time and amount of NAL delivered in the receptor was determined. Following promising results with solid MNs, for clinical translational purposes, a rapidly dissolving polymeric NAL loaded MN patch was fabricated, characterized, and evaluated for skin permeation. Results: The lag time for NAL permeation was significantly reduced across solid MN and laser treated skin than the untreated control. Micropore formation was verified using dye binding studies, scanning electron and confocal microscopy. A MN patch was fabricated and lag time of about 15 min was observed with a significantly higher drug flux of 15.09 ± 7.68 μg/cm²/h in the first 1 h as compared to the passive group (p<.05). Increasing MN length and density further enhanced the flux (p<.05). Through in-vitro in-vivo correlation, an optimized patch design that can reproduce the clinical pharmacokinetics of NAL obtained with commercial devices was predicted. Conclusions: A MN-based skin patch holds potential to deliver therapeutically relevant amounts of NAL for opioid overdose treatment.

Development of High Affinity-Peptide Fragments Targeting Amylin Receptors for Enhanced Pharmacotherapy

Sangmin Lee, High Point University, Fred Wilson School of Pharmacy. Objective: Human amylin is a peptide hormone that controls blood glucose and food intake. It exerts these physiological benefits by activating its cell-surface receptor, the amylin receptor. A peptide drug pramlintide targeting amylin receptors is available for diabetes treatment. The amylin receptor also holds a potential for obesity treatment since amylin receptor activation controls food intake. Despite recent structural achievement of amylin receptors, development of amylin receptor activators with enhanced affinity/potency has been under-explored. The objective of this study is to develop peptide ligands with enhanced affinity for amylin receptors towards more effective pharmacotherapy for metabolic diseases. Methods: Amylin receptor extracellular domains (ECDs) with a peptide-binding pocket were purified from mammalian cells. The purified amylin receptor ECDs were used for fluorescence polarization peptide-binding assay. First, alanine-scanning mutagenesis was applied to an amylin fragment to investigate which amino acids of amylin are critical for amylin receptor ECD binding. Then, other mutations were introduced to the amylin fragment to achieve affinity enhancement for amylin receptor ECDs. Results: Several mutations of the amylin fragment were found to significantly increase the affinity for amylin receptor ECDs: L27W, P29R or P29K, S34P, and Y37HYP (HYP: hydroxyproline) mutations. Interestingly, mutations of P28 to bulky, hydrophobic, or positively charged amino acids did not significantly change the affinity of the amylin fragment. When all the mutations were combined, the affinity of the amylin fragment was markedly increased by at least over 100-fold for amylin receptor ECDs. Conclusions: Affinity-enhancing mutations of the amylin fragment could be considered for developing next-generation peptide drugs targeting amylin receptors with enhanced affinity/potency.

Evaluation of an APPE Well-being Promotion (WelPro) Program

Tram Cat, University of California, San Francisco, Shareen El-Ibiary, Midwestern University, College of Pharmacy, Kelly C. Lee, University of California, San Diego. Objective: To evaluate the WelPro program on burnout in APPE students and assess attitudes and self-efficacy of Conference Leaders (CLs) after completing WelPro training. Methods: A longitudinal cohort study evaluating the impact of WelPro, comprised of individual- and organizational-level interventions, was conducted in
Class 2021PT (Pathway: 4-year traditional curriculum; Transformation: a 3-year curriculum) students. The primary aim was to evaluate the change in emotional exhaustion (EE) scores of Class 2021PT from beginning of year (BOY) to end of year (EOY) using Maslach Burnout Inventory-Human Services Survey for Medical Personnel [MBI-HSS (MP)]. The secondary aims were to compare EE scores between Class 2021P and Class 2020P (control group) students using MBI-HSS (MP) and assess CLs’ attitudes about burnout and self-efficacy in Assisting Students in Distress (ASD) via a 20-item survey. Independent and paired t-tests were used to evaluate MBI scores. Descriptive statistics were used to characterize attitudes and self-efficacy; Wilcoxon signed-rank and Mann-Whitney U tests were used for non-parametric ordinal data. Results: No differences in EE scores were observed for paired Class 2021PT from BOY to EOY and between Class 2021P and Class 2020P. All CLs believed burnout within the pharmacy profession could be avoidable. After completing the WelPro training program, confidence levels of CLs significantly improved in the identification of students in distress (p = .004), identification of resources for students (p = .016), and recognition of when and how to refer students in distress (p = .008 and p = .004). Conclusions: WelPro did not affect students’ EE scores. Results from the WelPro training program for CLs, however, appear promising. It can serve as a model for similar wellness training programs that directors and preceptors in experiential education can implement at their institutions.

**In Vitro Efficacy of Penicillin Plus Ceftriaxone Against Enterococcus Faecalis**

Jaclyn A. Cusumano, Long Island University, Zeel Shah, Long Island University, Ruhma Khan, Long Island University, Vanthida Huang, Midwestern University. **Objective:** Treatment of Enterococcus faecalis with penicillin plus ceftriaxone is a promising alternative to standard of care ampicillin plus ceftriaxone due to the better stability of penicillin compared to ampicillin. The central hypothesis was that penicillin plus ceftriaxone will have in vitro activity equivalent to ampicillin plus ceftriaxone due to the better standard of care ampicillin plus ceftriaxone due to the better activity. Further research is warranted to determine the clinical efficacy of penicillin plus ceftriaxone.

**Nisin ZP for Non-Small Cell Lung Cancer (NSCLC) Treatment: In Vitro Activity and Formulation Development**

Suyash Patil, St. John’s University, Nitesh K. Kunda, St. John’s University. **Objective:** Nisin ZP, an anti-microbial peptide (AMP) produced by the bacterium Lactococcus lactis, has demonstrated anticancer activity in preclinical reports. In this study, we evaluated anticancer potential and underlying mechanisms of nisin ZP in NSCLC cells. Further, we formulated a nisin ZP dry powder using spray-dryer to facilitate inhaled delivery. **Methods:** The in vitro cytotoxicity was evaluated using MTT assay in NSCLC (A549) and healthy (HEK293) cells. In addition, apoptosis, cell cycle, mitochondrial membrane potential, and reactive oxygen species (ROS) assays were performed to determine the mechanism of action. The wound healing, clonogenic, and spheroid assays were conducted to support the application of AMP in NSCLC. Nisin ZP (30% w/w) was spray-dried with mannitol, L-leucine, and trehalose (75:15:10) using Büchi mini spray-dryer B-290. Spray-dried powder was characterized for yield, peptide content, residual moisture, solid-state properties, and aerosolization performance. **Results:** Nisin ZP induced selective toxicity in cancer cells compared to healthy cells after 48 h. Nisin ZP exposure to A549 cells induced apoptosis and arrested cell cycle progression in G0/G1 phase. The cancer cell proliferation was inhibited via non-membranolytic pathways by mitochondrial membrane depolarization and elevation in intracellular ROS levels. The clonal expansion and wound healing of cancer cells was inhibited by nisin ZP treatment. Also, spheroid growth and 3D cell viability of A549 cells were significantly inhibited, suggesting excellent antitumor potential. The spray-dried nisin ZP formulation
was amorphous in nature and produced a yield of 62.0±
4.2% w/w, peptide content of 326.6±16.3 μg/mg, and
residual moisture < 3.0% w/w. Aerosolization studies indi-
cated aerodynamic diameter of 1.12±0.21 μm and fine par-
ticle fraction of 92.19±0.71%. Conclusions: Nisin Z
exhibits excellent anticancer efficacy against NSCLC and a
spray-dried powder formulation enables its inhaled delivery.

Novel Combination Therapy for Obesity-Induced
Cognitive Dysfunction
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Wei-Xing Shi, Loma Linda University, Johnny Figueroa,
Loma Linda University School of Medicine. Objective:
To examine whether lorcaserin (LOR) and beta-histidine
(BET) combination treatment enhances mesocortical
dopamine neurotransmission and ameliorates cognitive
dysfunction in a diet-induced obesity (DIO) rat model.
Methods: Adult Wistar rats were given either standard
chow or obese-genic diet for 8 weeks and subjected to a
battery of cognitive behavioral tests (Y maze, novel object
recognition and object-in-place [OIP]). Thereafter, they
were given either vehicle or drugs (LOR 2 mg/kg; BET
5 mg/kg; LOR [2 mg/kg] + BET [5 mg/kg]) for 30 days
while being maintained on their respective diets. Following
30 drug treatment days, the animals were re-tested for
cognitive functions. Electrophysiological recordings were
performed to examine effects of drugs on prefrontal cortex
(PFC) and dopamine neurons. Results: DIO rats showed
significant increase in body weight compared to control
diet (CD) rats. They also performed poorly in the OIP
task, but not Y-maze and novel object recognition tests.
Neither low dose LOR (2 mg/kg) nor BET (5 mg/kg)
improved OIP scores in DIO rats. Combination LOR + BET
treatment significantly increased OIP score of DIO rats to
the level of CD rats. The number of spontaneously active
dopamine neurons in the ventral tegmental area of DIO rats
were lower compared to CD rats. LOR + BET treatment
increased the number of spontaneously active dopamine
neurons in DIO animals. The functional connectivity analy-
sis showed difference between DIO and CD rats. LOR +
BET treatment produced a slight change on PFC-dopamine
neuron functional connectivity in DIO rats. Conclusions:
LOR + BET treatment significantly improved obesity-
induced cognitive dysfunction by restoring dopamine neu-
ron activity. Further studies are needed to determine the
mechanism of action of LOR + BET and its potential in ame-
liorating the neurocognitive consequences of obesity.

Optimizing the Treatment of Polymicrobial
Wound Infections
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University, Brian Tsuji, University at Buffalo, The State
University of New York. Objective: Pseudomonas aerugi-
nosa (PA) and Staphylococcus aureus (SA) are often cul-
tured together from polymicrobial wound infections. The
objective of the current study was to evaluate if PA is
capable of protecting SA from linezolid exposure, and
also determine if linezolid will increase the killing of PA
from the host defense peptide LL-37. Methods: Six iso-
lates were investigated. COL (SA) and PA01 (PA) are lab-
atory strains, whereas SA1-PA1 and SA2-PA2 are clinical isolate pairs collected from polymicrobial wound
infections. Using a starting inoculum of 10^6 CFU/ml of
each organism, 24-hour time-killing experiments were
conducted in duplicate using a linezolid concentration
array. Each SA isolate was investigated alone and during
co-culture with each PA isolate. A Hill-type mathematical
model quantified the potency (EC50) and maximal killing
of linezolid. In addition, the survival of each PA isolate
was evaluated after two hours of exposure to 25mg/L of
LL-37 peptide and varying concentrations of linezolid.
Results: The maximal killing of linezolid against each SA
isolate was not altered by the presence of any of the PA
isolates (Hill-type model analysis, p>0.05). The potency
of linezolid decreased slightly when COL was cultured
with PA2 (EC50 1.48mg/L, 95% CI 1.32–1.64mg/L) in
comparison to monoculture (EC50 1.17mg/L, 95% CI
1.06–1.29mg/mL), but otherwise PA did not alter the
potency of linezolid (Hill-type model analysis, p>0.05).
The survival of PA during exposure to LL-37 was not
impacted by the presence of up to 64mg/L of linezolid
(Mann-Whitney U Test, p>0.05). Conclusions: Pending
future in vivo studies, these results suggest that although
linezolid does not appear to sensitize PA to removal by
host defense peptides, the agent may be an effective anti-
staphyloccocal to use during polymicrobial infections.

Preceptor Perceived Barriers and Facilitators to
Assessing Advanced Pharmacy Practice Experience
Interprofessional Observations
Amanda Margolis, University of Wisconsin-Madison,
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of Pharmacy, Beth Martin, University of Wisconsin-
Madison School of Pharmacy. Objective: The validated
individual Teamwork Observation and Feedback Tool (iTOFT) was implemented in 2018 into required acute and ambulatory care Advanced Pharmacy Practice Experiences (APPEs) to assess student performance on interprofessional teams. It received mixed preceptor reactions. The objective of this project was to identify barriers and facilitators to the iTOFT activity and propose solutions to improve the activity. Methods: Preceptors on required acute or ambulatory care APPEs who submitted at least four iTOFT evaluations were invited to participate in a series of focus groups. Following focus group analysis, preceptors from each practice setting were asked to participate in one-on-one interviews to explore ways to improve the iTOFT activity. Verbatim transcripts were analyzed using inductive thematic analysis to identify patterns and themes across the data. Results: Four focus groups were conducted with preceptors, two with acute care (n=6) and two with ambulatory care pharmacists (n=9). Five pharmacists participated in interviews. A total of 11 barriers were identified in the focus groups which were abstracted into three themes: difficulty finding appropriate experiences, difficulty in using iTOFT, and student expectations. Identified facilitators to completing iTOFT included the value preceptors placed on assessing interprofessional skills, incorporating multiple student observations, simulating interprofessional interactions, understanding the tool is formative, and setting student expectations. Suggestions for improved use of iTOFT included considerations of overlapping items, frequency of occurrence in practice, and duplication of items with other assessments. Conclusions: Preceptors valued the assessment activity. Facilitators identified can be shared with preceptors to improve the process of evaluating student performance on interprofessional teams. The preceptor suggestions for improvement can help other schools and colleges modify their interprofessional assessment activities.

Student Professional Success is More Than What You Think it is

Benjamin D. Aronson, Ohio Northern University, Akua Appiah-Num Safo, University of Minnesota, Kristin Janke, University of Minnesota. Objective: To explore student perceptions of professional success. Methods: Interviews and focus groups were conducted using videoconferencing and recorded in spring 2021 with students from 2 schools in all 4 professional years. Audio files were transcribed verbatim. Transcripts were unitized by one researcher, and inductively coded by two coders per transcript. First cycle coding included process, values, and emotions coding. In a second cycle, a mix of pattern, axial, causation, elaborative, and focused coding were used. Codes were summarized around themes, connected to relevant theory/constructs/literature, and used to create student vignettes representing key features of the findings. Results: A total of 38 students participated in 20 sessions, resulting in nearly 15 hours of audio and approximately 280 pages of text. Success was defined in a variety of ways and participants emphasized that success is different for each student. Feelings of success were tied to feelings of pride, desire to do more, burgeoning confidence, relief, and of belonging (ie, “I’m good enough to be here”). Conceptions of success matured over time, from academic performance towards mastery of content that can be applied to patient care, signifying their emergence as skilled practitioners. Some students recognized their success through a feeling of personal achievement. For others, success was not often realized until they received external validation. Conclusions: Academic measures are insufficient, and at times, inconsistent with student definitions of professional success. These findings provide educators and administrators with insights that can be operationalized to help students recognize and achieve success, including considerations around the type of feedback provided, intentional recognition of achievement, aiding students in goal setting and mindset, and connecting learning to patient care early.

Tamoxifen-peptide Nanostructures for Efficient Intracellular Delivery

Amir Shirazi, Marshall B. Ketchum University. Objective: To fabricate a peptide-based drug delivery system containing 11 amino acids, to investigate its capability to bind with an anticancer drug, tamoxifen, and to evaluate its potential to transport tamoxifen intracellularly. Methods: The cyclic peptide containing eleven amino acids [CWRWRWRWRWR] was prepared by Fmoc/tBu solid-phase peptide synthesis. The formation of tamoxifen-peptide nanoparticles was performed in Water/DMSO (90:10) solution. The [(WR)5C]-tamoxifen samples for Transmission Electron Microscopy (TEM) were prepared by placing a drop of original solution (1 mM) on an carbon type-A 400-mesh copper grid. The Zeta Potential method was employed to measure the surface charge of [(WR)5C]-tamoxifen nanoparticles. The cytotoxicity of [(WR)5C] was tested in human leukemia cells, CCRF-CEM (50,000) cells in 96-well plates. The internalization of tamoxifen was evaluated in the presence and absence of [(WR)5C] using flow cytometry method. A model experiment was performed using a fluorescence derivative of the drug in CCRF-CEM cells in 6-well plates. Results: The formation of [(WR)5C]-tamoxifen was carried out in aqueous solution. TEM images showed that [(WR)5C]-tamoxifen formed nanosized structures with an approximate size of...
~250 nm after one-day incubation. The Zeta Potential results showed that the surface positive charge of [(WR)5C] reduced after binding with tamoxifen from 40 mV to 20 mV. The cytotoxicity of [(WR)5C] (50 μM) was found to be less than 5% in CCRF-CEM cells after 24 h of incubation. Flow cytometry result exhibited that the cellular uptake of a fluorescence labeled tamoxifen derivative was enhanced by 2 folds compared to that of the drug alone. **Conclusions:** [(WR)5C] and tamoxifen forms nano-sized complexes through non-covalent interactions. Our investigation offered that [(WR)5C] could serve as a potent nano delivery system for tamoxifen as a cargo drug.

**Validity and Usefulness of an Exposure Score and Profile for Chronic Pain Management.**

David R. Axon, The University of Arizona, Darlena Le, The University of Arizona, Jonathan Chien, The University of Arizona, Marion Slack, The University of Arizona. **Objective:** Chronic pain patients use a wide variety of pharmacological and non-pharmacological management strategies. The Chronic Pain Profile (CPP) is a tool for documenting all types of strategies with level of use based on patient self-report. To assess the validity and usefulness of the CPP, pharmacists rated and commented on the usefulness of the CPP. **Methods:** An online survey was administered to pharmacists to assess the clinical usefulness of the CPP using numerical items (scores ≥50% useful) and Likert scales (scores ≥4 useful). Functionality was assessed via open-response items. Qualitative analysis was conducted by two independent researchers who coded the comments and identified key themes through consensus. Content validity was evaluated by comparing participant management strategies to strategies previously identified in the literature; strategies were considered valid if previously identified. **Results:** Data were collected for 33 individuals (female=64%, age ≥50=54%, white=64%). Mean usefulness scores ranged from 66.6±22.4 to 80.9±23.5 and three of the five ordinal-level items had a median score of ≥4. Three key themes were identified: Enhancing the CPP’s usability; Favorable CPP features; and CPP utilization. All identified strategies matched with strategies from the literature (mean per person with chronic pain=9±4). **Conclusions:** The CPP was determined to be clinically useful and to have content validity indicating that the CPP could provide a valid method of collecting and reporting on the number and types of pain management strategies with level of exposure for each strategy used by patients with chronic pain. Further data are needed to assess construct and criterion validity.