Category: Early Stage Investigator

The Prevalence of Polysubstance Use among Psychiatric and Emergency Department Patients in West Virginia

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Aim: In 2017, 11.8 million people in the U.S. misused opioids with more than 63,000 deaths nationally. West Virginia continues to have the highest drug overdose mortality in the nation with 58 deaths per 100,000 population, well ahead of all other states. The purpose of this study was to assess the rate of polysubstance use.

Methods: In this retrospective study utilizing the WVU Medicine electronic medical record data repository, deidentified data were extracted from the following healthcare encounters: inpatient psychiatric admissions, psychiatric outpatient visits, and emergency department visits between 2009 and 2017 among persons who had been diagnosed with opioid use disorder (OUD) who had a positive urine toxicology for opioids at the time of the initial encounter with the healthcare system.

Results: A total of 3,032 persons met the inclusion criteria, 77% of which were polysubstance users. Across the entire sample, 40% were positive for opioids and one additional substance, 26% were positive for opioids and two additional substances, and 12% were positive for opioids and three or more additional substances. Benzodiazepines were the most common co-occurring substance, 43% among all patients. Cannabis and cocaine were the second and third most common co-occurring substance (36% and 21%, respectively). Among ED admissions, 209 were diagnosed with substance toxicity/overdose; of those, 55% were positive for benzodiazepines, 33% for cannabis, and 26% for cocaine.

Conclusions: These data demonstrate that the current substance use epidemic in the U.S. extends well beyond opioids, suggesting that comprehensive substance use prevention and treatment strategies are needed.

Category: Early Stage Investigator

Clinical Outcomes and Screening Rates of Infants Born to Women with Active Hepatitis C Infection

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Background: West Virginia (WV) has the highest rate of Hepatitis-C infection (HepC), especially in young persons with injection drug use. Young pregnant women can transmit the virus to the infant. Yet, current guidelines do not recommend universal screening until 18 months of age for infants born to HepC positive mothers.

Purpose: This study investigates profiles of infants born to mothers with active HepC, including evidence of Neonatal Abstinence Syndrome (NAS) and results of umbilical cord drug screening, and determines whether HepC screening matches current guidelines.

Methods: We performed a retrospective chart review of infants born from January 1, 2008-December 31, 2017 at WVU Medicine to mothers with laboratory confirmed HepC. Data were analyzed for descriptive statistics for demographic and clinical profiles of infants. Bivariate logistic regression analyzed the association between presence of drugs in umbilical cord and neonatal intensive care unit (NICU) admission.

Results: There were 209 births during the ten year period, of which 55.5% were males, 82.3% covered by government health insurance, 37.3% delivered by C-section, 31% had an additional hospitalization aside from delivery, almost half admitted to NICU, 70.8% diagnosed with NAS, and 27.3% tested for more than one drug in umbilical cord. The odds of infants with drugs detected in umbilical cord were significantly higher for NICU admission than infants without drugs. Only 8.1% were screened for HepC within 18 months of birth.

Conclusion: WV infants born to women with active HepC have high rates of NAS, NICU admission, and do not receive recommended HepC screening.

Category: Senior Investigator

Genetic factors that influence Neonatal Opioid Withdrawal Syndrome (NOWS) in a WV cohort

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In 2017, 13% of neonates born in WV were opioid exposed in utero. A third of these patients had NOWS, characterized by central, autonomic and enteric nervous system dysfunction. Mild NOWS is treated by therapeutic handling, while more severe NOWS is treated with opioids. To date, predicting the risk of NOWS and the long term consequences is not possible. In adults, genetic variation within opioid signaling pathways predicts addiction and withdrawal; limited target gene studies in the NOWS population show similar trends. We hypothesize that NOWS severity is in part due to variants in genes involved in the metabolism of, and response to, opioids, and in genes related to brain development. In this study we recruited patients from MU and WVU MAT pregnancy programs and compared the genetic profiles of maternal-neonate dyads based on the need to treat NOWS pharmacologically. In our study population, 38% of the neonates required pharmacological interventions to treat their NOWS and had a significantly longer length of stay than non-treated (45 +/- 15 days compared to 7 +/- 3 days, $p<0.05$ Students t test). Analysis indicated 49 maternal and 36 neonatal genetic variants significantly associated with NOWS. In the maternal variants, we identified gene polymorphisms linked to anxiety and depression which increased the risk of NOWS. This includes a polymorphism in NPSR1, which has previously been linked to somatization of anxiety. It is thus possible that NOWS is linked to an exaggerated maternal response to stress, anxiety, and addiction, promoting neonate somatic symptoms in NOWS.

Category: Student/Resident/Fellow

Implications of Drug Use Disorders on Spine Surgery

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Introduction: The opioid crisis has been declared a “public health emergency” and the CDC has included opioid overdose prevention as a top five public health challenge. The purpose of the study was to investigate the outcomes of patients with substance abuse disorder who undergo spine surgery.

Methods: A retrospective chart review was performed on patients with drug abuse who underwent non-elective spine surgery by orthopedic or neurosurgical staff from 2012 to 2017 at a level one trauma center and spine referral center.

Results: A total of 49 patients undergoing 72 surgeries were reviewed. The most common type of drug abuse was opioids (44/49 patients; 90%). Of 31 patients (63%) abusing several drugs, 29 included opioid abuse. The most common indications were infection (26/49, 53%) and trauma (13/49, 27%). 29% (14/49) of patients had complications, the most common being hardware failure (7/49, 14%). 20% (10/49) of patients left against medical advice and 22% (11/49) did not follow up after hospital discharge. The average length of hospital admission was 22 days. 45% (22/49) of patients were known to be in a drug program pre-operatively versus 39% (19/49) post-operatively. 65% (32/49) were prescribed opioids in the immediate post-operative period and 47% (23/49) continued to abuse drugs post-operatively.

Discussion: Patients with drug abuse history are a unique population at increased risk of peri-operative complications and inadequate post-operative follow-up. Additional studies are warranted to determine whether additional peri-operative education, psychiatry consultations, or prescription of opioid addiction treatment regimens will improve drug use cessation and outcomes.

Category: Senior Investigator

Selective Vulnerability of Somatostatin-Containing Interneurons in Early Alzheimer's Disease

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Alzheimer's disease (AD) is a devastating, progressive dementia with no known prevention or cure. All efforts to-date to reverse or arrest disease progression have failed, possibly because they were applied too late in the process, when irreversible damage to cortical networks has already occurred. Thus, a better understanding of the earliest, presymptomatic stages of the disease is critically needed if we are to develop successful interventions.

A consistent finding, in both humans and mouse models of the disease, is specific loss of somatostatin-containing (SOM) inhibitory interneurons and synapses in the cerebral cortex. We hypothesized that the normal functioning of SOM interneurons is disrupted very early in the progression of AD, well before the neurons die and before any of the histological or behavioral manifestations of the disease are evident, and that this dysfunction plays a facilitatory or even obligatory role in AD progression. If so, then early interventions which prevent SOM interneuron dysfunction would be highly promising as anti-AD therapies.

Using electrophysiological recordings in brain slices, we characterized functional changes in SOM interneurons in a transgenic mouse model which expresses a human amyloid precursor protein with familial AD mutations. We found a ~50% decrease in the minimal current level generating an action potential, compared with WT littermates, implying a *doubling* of the intrinsic excitability of these interneurons. A possible outcome could be increased Ca^{2+} influx, eventually triggering excitotoxic cell death. To our knowledge this is the report of profound changes in intrinsic physiology of inhibitory interneurons in pre-symptomatic AD mice.

Category: Student/Resident/Fellow

Tobacco Abuse is a Strong Risk Factor for Adrenal Cortical Carcinoma

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BACKGROUND: Smoking has been suggested as a risk factor for adrenal cortical carcinoma (ACC), but, due to the rarity of this tumor, this hypothesis has only been inferred from single study using a mixed population of adrenal tumors that included pheochromocytoma and neuroblastoma as well as ACC.

METHODS: De-identified IRB exempted records were analyzed for age, gender, and smoking history in adult patients diagnosed with ACC in both the West Virginia University database containing 2,699,193 patients and, in the larger TriNetX database of 21,426,477 patients from 2008-2018. In addition, the statewide ratio of smoking to ACC prevalence was computed in all 50 states using data from SEER and the CDC.

RESULTS: Given the high rate of both tobacco use and ACC in the West Virginia Health System, we hypothesized that smoking contributed to increased prevalence of ACC in our state. We compared the rates of ACC and smoking in all 50 states using data from SEER. Among the 50 states, West Virginia had the highest smoking rate and the second highest rate of ACC. Utah had the lowest rate of smoking and the third lowest rate of ACC. The sample correlation between statewide smoking and ACC is .4177 indicating a significant association between the two (p=.0035). From 2008 to 2018, 20 patients with ICD10 code c74.0 (ACC) were abstracted from our EMR system. Examination of the individual charts determined 15 of the 20 patients had confirmed ACC diagnosis. This cohort was compared with matched age and gender matched controls. In the control group, there 13.3% were smokers while in the ACC group, 60% were smokers. The difference is significant (p=.0005) (OR)=9.75 (95% CI; (2.54, 37.38). We next reviewed the larger TriNetX database and found that the prevalence of smoking in the ACC group to be 35.2% as compared to 9.0% in the TriNetX group(p-value<.0001).

CONCLUSION: Our retrospective review strongly supports smoking as a major risk factor ACC. To our knowledge, this is the first study to demonstrate a strong association of smoking in a cohort of biopsy proven ACCs.

Category: Early Stage Investigator

Whole Blood Replacement Treatment Rescues Brain from Damage after Ischemic Stroke

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Stroke remains a major cause of morbidity and mortality, ranking as the fifth leading cause of death in the U.S. Current treatment of acute ischemic stroke focuses on immediate restoration of blood flow to the occluded vessel either pharmacologically with recombinant tissue plasminogen activators (rtPA), or mechanically via endovascular intra-arterial thrombectomy. Based on current guidelines, both therapies have their limitations, as only a certain subset of stroke patients meet the criteria for treatment, combined with a small therapeutic window of 4.5 hours to benefit from therapy. Thus, developing effective treatments for stroke remains a pressing need. We developed a study to provide evidence for a promising new therapeutic approach to stroke using whole blood replacement in the acute period following transient Middle Cerebral Artery Occlusion (tMCAO) in mice. We performed tMCAO on C57/BL6J mice and obtained donor blood from the same strain of recipients by cardiac puncture. Whole blood replacement was performed at 6 and 8 hours post-tMCAO. Blood was transfused through the femoral vein and released via femoral artery. We demonstrated that whole blood replacement overwhelmingly protects stroke mice from acute ischemic injury. Our results showed a pronounced significant decrease in infarct volume 23 hours post-tMCAO. We also demonstrated a profound decrease in neurological deficits at 23 hours in both treatment groups compared to the control group. Our study is the first to show that whole blood replacement profoundly decreases infarct size and leads to improved stroke outcomes. These results are extremely important in offering a new therapeutic strategy for the treatment of stroke that would extend the current treatment window and have profound potential impact on human clinical trials.

Disclosure: The study is provisionally patented by the Office of Innovation, Entrepreneurship, and Commercialization at the West Virginia University.

Category: Senior Investigator

Comparison of urban and Rural Umbilical Cord Thyroid Hormone Levels and Polycyclic Aromatic Hydrocarbons (PAHs) DNA Adducts

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Maintaining maternal thyroid function during pregnancy is critical for successful fetal development. Low thyroid hormone levels have been associated with respiratory distress in newborns. Furthermore, environmental compounds that are biotransformed by cytochrome P450 enzymes may form DNA adducts that may have detrimental effects on the newborn. The overall goal of this study was to compare thyroid hormone levels and quantitate PAH-DNA adducts from umbilical cord blood of children from urban and rural areas of West Virginia. This study may provide better understanding of the causes of increased health disparities individuals in urban and rural West Virginia. A comparative cross-sectional study was conducted on 172 babies born at Cabell Huntington Hospital. The babies were divided as 79 rural and 93 urban. Rural and urban locations were based on Rural-Urban Commuting Area Codes. Cord blood was collected at the time of delivery, maternal use of tobacco was recorded for each mother. Cotinine levels were measured as a biomarker for cigarette smoke exposure of the fetus. Umbilical cord blood was processed to isolate DNA and potential PAH-DNA adducts were analyzed by HPLC. T3 uptake was higher in the rural groups ($p=0.041$) than the urban samples. No differences were detected between urban and rural groups for TSH, free T4, free T3 or free T4 uptake. A total of 22 samples contained PAH-DNA adducts. A positive correlation was found for cotinine and DNA adducts. In summary, higher T3 uptake occurred in rural newborns; PAH-DNA adducts correlated with the presence of cotinine.