–Minneapolis VA Health Care System–
VA Research Day 2018

Frank A. Lederle III, MD 1952—2017
"A wonderful colleague, a prolific investigator,
a talented mentor and educator,
a devoted physician and a true friend to many"

Program and Abstract List
(alphabetically, by author)

May 16, 2018

VA | **U.S. Department of Veterans Affairs**

Veterans Health Administration
Office of Research and Development

☆ Dedication ☆

Frank A Lederle III graduated from Pomona College in 1974 and received his MD degree from the University of New Mexico in 1979. After completing a residency in Internal Medicine at the University of Minnesota (UMN), he accepted a position as a staff physician in the Minneapolis VA General Internal Medicine (GIM) Section with a faculty appointment at UMN. Dr. Lederle remained in that position until his untimely death in early 2018, advancing to the academic rank of full professor in 2000.

Dr. Lederle was recognized locally, nationally, and internationally as a leading scholar in the epidemiology, diagnosis and management of abdominal aortic aneurysm and for his expertise in clinical trial design. He was the Principal Investigator of 5 VA Cooperative studies and led the nationally funded Minneapolis Center for Epidemiological and Clinical Research between 2004 and 2009. In 2012 he became Director of the Minneapolis Network of Dedicated Enrollment Sites (NODES) initiative. In recognition of this outstanding record of achievement, Dr. Lederle won the John Blair Barnwell Award in 2017, the VA's highest award for clinical research.

Dr. Lederle was a trusted colleague, a dedicated physician and a much sought-after mentor. Many of his mentees went on to distinguished research careers, in recognition of which Dr. Lederle won the UMN Medical School Carole J. Bland Outstanding Faculty Mentor Award.

Dr. Lederle was passionate about clinical research and evidence based medicine and continued to enjoy his scholarly work and collegial professional interactions even as his health declined in the last 2 years of his life. Dr. Lederle and his family created the Frank Lederle Paper of the Year Award at the Minneapolis VA Medical Center's affiliated non-profit, the Center for Veterans Research and Education. He would have been thrilled to know that the first awardee is Dr. Erin Krebs, a junior colleague in GIM, who won the award for her article in JAMA, a very prestigious journal.

–Hanna E. Bloomfield, MD, MPH

☆Program☆

1. Oral Presentations – 1st Floor Auditorium (12:00 - 1:00 pm)

☆**Introductions and Welcome**.. Hanna E. Bloomfield, MD, MPH

Associate Chief of Staff, Research Service

☆**2018 Zieve Award Presentation**..James Johnson, MD

Recipient:
Arianne Baldomero, MD
"The Relationship Between Oral Health and COPD Exacerbations"

☆**2018 Lederle Award Presentation** ....Aasma Shaukat, MD, MPH

Janet Lederle

Recipient:
Erin Krebs, MD, MPH
"Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial"

JAMA 2018 319(9):872-882

☆**Keynote Address**.. Jakub Tolar, MD, PhD

Dean, University of Minnesota School of Medicine

☆ *The Center for Veterans Education & Research will be providing Free Box Lunches to the first 200 attendees.*

2. Poster and Exposition Session – 2nd Floor Flag Atrium (1:00 – 3:30 PM)

☆ *Research Findings and Innovations from the Minneapolis VA Health Care System*

☆ *Popcorn provided by the Minneapolis VA Research Office*

Author Index *(first author only)*

1. Implementation Analysis of a Radiology Dictation Template for Tracking Incidental Pulmonary Nodules

Aase, Allison [1,2]; White, Katie [1]; Fabbrini, Angela [2]; Melzer, Anne [2]

1. University of Minnesota School of Public Health
2. Minneapolis VA Health Care System

Abstract: Incidental pulmonary nodules (IPNs) are common, and tracking these nodules over time with CT decreases lung cancer mortality. Up to 70% of IPNs are not follow-up correctly. At the Minneapolis VA Health Care System, adherence to tracking guidelines is ensured through a multi-step process. Using structured reporting in radiology has been shown to reduce errors, so a template was implemented at the Minneapolis VA which includes all necessary nodule components of the new national standardized tracking guidelines. Using this standardized radiologist reporting system, pulmonary department nurse trackers make follow-up decisions using guidelines. This project used a mixed-methods approach. Radiology reports pre implementation (n = 400) and post implementation (n = 400) were reviewed from patients seen at the Minneapolis VA Health Care System who were enrolled in the lung nodule tracking program. Six nodule components were identified as necessary to determine proper follow-up: average diameter, location, density, number of nodules, suspicious features, and risk stratification. Presence of these in the reports was reviewed and analyzed using a paired t-test. Qualitative interviews with radiologists (n = 4) and lung nodule team trackers (n = 2) were conducted to understand their experience with the template and implementation. Transcripts of the interviews were manually analyzed using the Consolidated Framework for Implementation Research. There was significant improvement in the proportion of completed elements after the implementation of the dictation template (p < 0.001), primarily due to increased reporting in the characteristics of average density, number of nodules, suspicious features, and risk stratification. The template was used in approximately 40% of all radiology readings involving lung nodules. Lung nodule team trackers favorably viewed the template, and felt they were more autonomous in their roles when it was being used. Radiologists generally approved of the template, but this was not unanimous. Some radiologists described having a very close relationship with the pulmonary department, while others said that they feel there is a lack of communication for feedback and ongoing support. Overall, use of a dictation template may be effective in increasing compliance with IPN follow-up. Low utilization rates of the template may be combated through clearer communication throughout process improvement.

2. CSP #592 Efficacy and Safety of ICD Implantation in the Elderly

Adabag, Selcuk [1,2]; Buelt-Gebhardt, Melissa [1]; Tholakanahalli, Venkat [1,2]; Florea, Viorel [1,2]; Condon, Debra [1]; Nyugen, Jennifer [1]; Singh, Steven [3]

1. Minneapolis VA Health Care System
2. University of Minnesota
3. Washington DC VA Medical Center

Abstract: Implantable Cardioverter-Defibrillators (ICDs) prevent Sudden Cardiac Death (SCD) by restoring normal rhythm in the event of a life-threatening ventricular tachyarrhythmia. While ICD therapy is a proven preventer of SCD in younger patients, its ability to reduce all-cause mortality in those with advanced age is unclear. ICD therapy is considered to be an under-utilized treatment option despite widely recognized safety and efficacy. Age bias is a particularly prominent theory in the effort to explain under-utilization of ICD. In major clinical trials of patients receiving ICDs over the past 15 to 20 years, the mean and median age of study populations range from 50 to 65 years of age. The proportion of potentially eligible VA patients implanted with an ICD peaks at approximately 67 years of age and declines continuously thereafter. No randomized clinical trials have focused solely on an older population. The overall aim of CSP #592 is to study the safety and efficacy of ICD implantation as a primary prevention strategy of Sudden Cardiac Death (SCD) in patients 70 years of age and older. In particular, this study is designed to compare the effectiveness of ICD, in addition to Optimal Medical Therapy (OMT), on all-cause mortality versus OMT alone. OMT includes standard intervention for chronic heart failure patients, such as disease management with neurohormonal blockade, adoption of healthy diet, and exercise. One particularly important secondary objective is to assess treatment efficacy under the conditions of high versus low co-morbidity burden. In the study, participants are randomized (1:1 ratio) to ICD + Optimal Medical Therapy (OMT), or OMT alone, stratified by participating site and co-morbidity level (Charlson score < 3 versus > 3). Follow-up will occur every 6 months until study close. We postulate that ICD + OMT will result in a 25% reduction in the hazard for all-cause mortality.

3.   VA Cooperative Studies Program (VA CSP) Network of Dedicated Enrollment Sites (NODES)

Adabag, Selcuk [1]; Condon, Debra [1]; Donaire, Marti [1]; Kantorowicz, Alexandra [1]

1.   Minneapolis VA Health Care System

Abstract: The VA Cooperative Studies Program (VA CSP) Network of Dedicated Enrollment Sites (NODES) is a consortium of VA Health Care Systems that have facility-based teams dedicated to conducting VA CSP Research. The specific aims include; enhancing study performance and enrollment rates; provide a more consistent and comprehensive approach to CSP study management, quality and regulatory compliance at the VA Medical Centers; obtain center-level perspectives in the design and execution of studies; and provide opportunities for research personnel interested in supporting the VA CSP research mission. A Director, Manager, Administrator, and Research Nurse support these efforts at each individual NODES location. NODES shares facility-derived best practices and provides local insights to VA CSP partners for efficient management and conduct of all study activities. The following achievements reflect cumulative data of the NODES sites from October 2012 – Present: • Established cross-coverage on all open CSP studies • NODES staffing incorporated as part of local CSP study teams • Created Mentorship Program for new local study coordinators • Created procedures for mobile recruiting at CBOCs • Work stream meetings on improving study design & procedures • Beta testing case report forms • Enhanced recruitment through Mobile Recruiting Equipment • Reduced logistical and staffing barriers • Development of Partnership between NODES and Non-NODES facilities to assist in study teams with low recruitment • Publication in JAMA • Publication in Contemporary Clinical Trials Communications • Creation of VA CSP-NODES Executive Board

Research Topic: Health Systems
Funding agencies: CSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

4.   Defining Roles of Protein Kinase CK2 in Promoting Cancer Cell Survival via Mitochondrial Pathways

Ahmed, Khalil [1,2]; Kren, Betsy [1]; Trembley, Janeen [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Introduction: CK2 (previously termed Casein Kinase 2) is a protein kinase which demonstrates elevated expression and activity in all cancers examined. The heterotetrameric CK2 enzyme is comprised of two catalytic (α and α´) and two regulatory (β) subunits. Two major roles of CK2 are to promote cell proliferation and suppress cell death. The kinase is localized in various compartments of the cell; a subpopulation of CK2 is present within mitochondria, and the intra-mitochondrial function of CK2 in the context of normal and malignant cell survival remains to be determined. Our group demonstrated rapid loss of mitochondrial membrane potential and cell viability upon inhibition of CK2 activity in prostate cells, with greater effect observed in prostate cancer cells relative to benign prostatic hyperplasia cells. Results: We now present data suggesting that the intra-mitochondrial sub-population of CK2 is responsible for protecting membrane potential. Further, our data indicate that stable expression of increased CK2 protein levels in non-transformed cells contributes to increased mitochondrial network presence. Finally, we have observed that CK2 activity promotes mitochondrial biogenesis in cancer cells. Conclusion: Our data suggest new roles for CK2 in promoting cell survival and suppressing cell death with integral involvement of mitochondria.

Research Topic: Cancer
Funding agencies: BLR&D
Grant support: I01 BX001731

5.   Men with Urinary Tract Infections & Sub-Study about Bacterial Resistance to Antibiotics

Amundson, Carla [1]; Boersma, Peter [1]; Drekonja, Dimitri [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Background Inappropriate treatment of purported urinary tract infection (UTI) is a major cause of antimicrobial overuse. This is of particular concern because such treatment often involves fluoroquinolones and other agents active against Gram-negative organisms, thus driving resistance to the few orally-available drugs still active against these organisms. An ongoing randomized controlled trial of treatment duration for men with UTI provides a unique opportunity to prospectively assess the appropriateness of UTI diagnoses and subsequent antimicrobial therapy. Methods The main objective of this trial is to randomize men with UTI to 7 vs. 14 days of treatment with ciprofloxacin or trimethoprim/sulfamethoxazole and assess for differences in rates of symptom resolution. Potential cases of UTI among men presenting to outpatient clinics and the emergency department of the Minneapolis VA Healthcare System are identified by diagnostic codes and prescriptions for the studied antimicrobials. Subsequently, medical record review and phone contact (if needed) are used to determine trial eligibility–including manifestations of UTI. Qualifying UTI manifestations include dysuria, frequency, urgency, hematuria, and flank, suprapubic, or perineal pain. Results From 4/14/2014 through 4/10/18 there were 2,725 unique visits in which a man was diagnosed and treated for a UTI. A total of 759 (27.9%) had no manifestations of UTI, but still received antimicrobial therapy. Among the 1,966 men with symptoms (72.1%), 578 (29.4%) met eligibility criteria, and 144 (24.9% of eligible) enrolled. Conclusions Screening for this trial of treatment duration of male UTI allows prospective screening for manifestations of UTI, with patient contact for encounters with no (or inconsistent) documentation of signs or symptoms. We documented a high rate of misdiagnosis and inappropriate antimicrobial treatment, contributing to the emerging antimicrobial resistance crisis.

Research Topic: Infectious Diseases

6.   Is Chronic Inflammation the Underlying Cause of Gulf War Illness?

Bach, Ronald [1,2]; Butterick, Tammy [1,2]; Trembley, Janeen [1,2]; Nixon, Joshua [1,2]; Slater, Billie [1]; Leis, Linda [1]; Rector, Thomas [1,2]; Johnson, Gerhard [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Background: Many U.S military personnel who served in the 1990-91 Gulf War suffer from an unexplained deployment-related chronic multisystem illness (DRCMI), a.k.a. Gulf War Illness (GWI). GWI symptoms include chronic fatigue, musculoskeletal pain, impaired cognition (mood & memory problems), gastrointestinal disorders, and skin rashes. DRCMI is beginning to emerge as the signature adverse health outcome, not cause by combat trauma, in Veterans of Post-9/11 Operations in Iraq and Afghanistan. When compared to GWI, the onset of DRCMI symptoms in Post-9/11 Veterans is occurring earlier and at a higher rate. Goals: Validate Translational Research Paradigm (Bench to Bedside in 3 Steps) • DISCOVER biomarkers of GWI in blood using proteomics analysis of plasma and a complete blood count with differential (CBC diff) • IDENTIFY a therapeutic target from the blood biomarker fingerprint • TEST an evidence-based intervention in a clinical trial Methods: • Surveillance study of 85 Gulf War Veterans • 57 GWI+ and 28 GWI- subjects by CDC 10 criteria (Fukuda case definition) • Performed CBC diff and immunoassays of 61 plasma proteins • Statistical analyses: Mann-Whitney rank sum test to compare biomarker distributions and stepwise logistic regression to formulate a diagnostic model. Results: • Lymphocytes, monocytes, neutrophils, & are platelets elevated in GWI+ subjects • Four plasma proteins are higher (C-reactive protein, leptin, brain-derived neurotropic factor, matrix metalloproteinase-9) and two are lower (metalloproteinase-2 and fatty acid binding protein 3) in GWI+ subjects • A diagnostic model of three biomarkers–lymphocytes, monocytes, and C-reactive protein–had a predicted probability of 90% (CI 76-90%) for diagnosing GWI when the probability of having GWI was above 70% Conclusions: • Quantification of inflammation-related plasma proteins and cellular enumeration provide objective criteria for the diagnosis of GWI • All 11 elements of the GWI biomarker fingerprint point to chronic inflammation as the underlying cause of GWI and an evidence-based therapeutic target • Gulf War Illness Inflammation Reduction Trial, ClinicalTrials.gov #NCT02506192) is being conducted to determine if reducing inflammation with delayed-release prednisone is an effective treatment for GWI (scheduled completion May 2019)

Research Topic: Gulf War Veterans Illness

7.   The Relationship Between Oral Health and COPD Exacerbations

Baldomero, Arianne [1]; Siddiqui, Mariam [1]; Lo, Chia-Yin [2]; Petersen, Ashley [1]; Connett, John [1]; Kunisaki, Ken [1]; Wendt, Chris [1]

1.   University of Minnesota
2.   Minneapolis VA Health Care System

Abstract: INTRODUCTION: Poor oral health has been implicated as an independent risk factor for COPD, however, very few studies have evaluated the association between oral health and COPD exacerbations. We aimed to determine the association between poor oral health status and both COPD exacerbations and respiratory health status. METHODS: Using a case-control design, we assessed the 1-item global oral health assessment, 5-item Oral Health Impact Profile, dental symptoms, dental habits, and St. George's Respiratory Questionnaire (SGRQ). Cases were patients with frequent exacerbations defined as = 1 exacerbation in the previous 12 months, while controls were patients with no exacerbations in the previous 24 months. Patients were contacted via phone interview or in-person visits at the Minneapolis VA Medical Center. In a subset, we additionally performed dental exams to measure bleeding on probing, probing depth, clinical attachment loss, periodontitis severity, plaque index, gingival index, and carries risk assessment. We evaluated associations between oral health and COPD exacerbation status using logistic regression, adjusted for smoking status, educational attainment, and inhaler use. Linear regression was used to assess relationships between oral health and SGRQ scores. RESULTS: Controls (infrequent exacerbators, n = 118) were significantly more likely to have < 4 teeth, compared to cases (frequent exacerbators, n = 100) (44% vs. 30% respectively; p = 0.046). Self-reported oral health status and dental exam measures did not vary significantly between cases vs. controls. However, the odds of severe COPD exacerbations requiring hospitalizations and emergency department visits were consistently higher in those with worse dental exams compared to those with milder COPD exacerbations. Worse oral health status was strongly associated with worse SGRQ scores. CONCLUSIONS: Although oral health status was not related to COPD exacerbation status, it may be related to severity of COPD exacerbations. Infrequent exacerbators were more likely to have < 4 teeth. Better oral health status was associated with better respiratory health status. Oral/dental interventions represent a novel non-pharmacologic COPD treatment that requires further testing.

8.   Exoskeleton Assisted Walking in Patients with Spinal Cord Injury: Impact on Quality of Life

Boyle, Stephanie [1]; Eddy, Byron [1]; Wolf, Allison [1]; Schieffer, Chris [1]; Stien, Crystal [1]; Sauerbrey, Bethany [1]; Sauerbrey, Matthew [1]

1.   Minneapolis VA Health Care System

Abstract: The purpose of this study is to determine the effects of exoskeletal-assisted home and community walking on quality of life of Veterans/active duty military service members with spinal cord injury (SCI). This study is a randomized, clinical trial consisting of two groups: the Intervention group, consisting of individuals who will be trained and provided an exoskeleton for home/community use for 4 months, and the Control group, who will continue using their wheelchair for usual lifestyle activities for 6 months. The goals of this study are to determine the effect of being able to walk in the home/community (using EAW) on quality of life, and changes in physical, mental, and social well-being. Since EAW will provide a new form of physical activity, the study will also evaluate changes to the amount of fat tissue in the body, the body's ability to regulate blood sugar, and cholesterol profiles. As one of the ten sites that are participating in this trial, the Minneapolis VA Medical Center hopes to communicate the groundbreaking nature of the study, and advertise for participation.

9. **Microglial FABP4-UCP2 axis modulates neuroinflammation and cognitive decline in obese mice**

Butterick, Tammy [1,2]; Duffy, Cayla [1,2]; Xu, Hongliang [2]; Bernlohr, David [2]; Lee, Michael [1,2]; Nixon, Joshua [1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Background: Midlife obesity is a risk factor for metabolic syndrome and cognitive disorders such as Alzheimer's disease (AD). Obesity is also characterized with chronic low grade hypothalamic and hippocampal neuroinflammation. We have shown that the fatty acid binding protein 4-uncoupling protein 2 (FABP4-UCP2) axis plays a key role in fatty acid lipid metabolism and neuroinflammation. Specifically, loss of FABP4 inhibits saturated fatty acid-induced activation of microglia, triggering neuroinflammation and cognitive decline. Hypothesis: Diets high in saturated fatty acids induce microglial metabolic adaptations promoting neuroinflammation and subsequent cognitive decline. Methods: We evaluated cognition in high fat diet (HFD)-fed mice lacking microglial FAPB4 (FABP4/ap2, AKO). Fifteen-week-old male AKO and wild type (WT) mice were maintained on 60% HFD or normal chow (NC) for 12 weeks. Working and spatial memory were assessed using several cognitive tests (Barnes maze and T-maze). To evaluate metabolic functions, we conducted *in vitro* studies used mouse microglial cultures with either FABP4 inhibitor (HTS01037), ± saturated fatty acid stimulation (palmitic acid) or ± genetic inhibition of UCP2. Results: WT mice maintained on HFD presented with impaired long and short -term memory, while AKO mice were unaffected. Brain tissue analysis showed decreased neuroinflammation (Iba-1, TNF-α and Irg-1 gene expression) and increased UCP2 gene expression in AKO mice relative to WT controls. In microglial cultures, loss of FABP4 resulted in an anti-inflammatory phenotype. Further, pharmacological inhibition of FABP4 reduced inflammatory cytokines (such as TNF-α and IL-6) in fatty acid stimulated WT microglia. Conversely, loss of UCP2 increased microglial reactive oxidative stress and potentiated inflammation. Conclusions: Hypothalamic inflammation contributes to metabolic dysregulation and the onset of obesity. Collectively, our work supports that the FABP4-UCP2 axis represents a strategic therapeutic target in preventing diet-induced cognitive decline. Further work is necessary to understand the role of the FABP4-UCP2 axis in microglial immunometabolism within the context of obesity and brain health. Relevance to VA Health Care: 1: Research is focused on the targeted research for the treatment and prevention of obesity-related cognitive impairment. 2: Incidence of obesity and overweight are higher in Veterans than in the general US population.

Research Topic: Dementia & Neuronal Degeneration

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10. **Daily CoQ10 Administration Enhances Expression of Electron Transport Chain Proteins in Hibernating Myocardium**

Chappuis, Erin [1]; Hocum Stone, Laura [1]; Wright, Christin [1]; Ward, Herbert [1]; Kelly, Rosemary [1]; McFalls, Edward [1,2]

1. University of Minnesota
2. Minneapolis VA Health Care System

Abstract: INTRODUCTION: Our novel swine model of chronic hibernating myocardium is characterized by tissue with reduced blood flow and reduced function that remains viable. Our previous studies have shown that hibernating myocardium results in decreased expression of electron transport chain proteins and mitochondrial fusion proteins, suggesting that the functional impairment may be due to mitochondrial dysfunction. Clinical studies have suggested a beneficial effect of chronic administration of Coenzyme Q10 (CoQ10) in ischemic heart disease. We tested the effect of administration of dietary CoQ10 in swine with established hibernating myocardium. METHODS: Twelve pigs underwent placement of a constrictor around the LAD artery and established hibernating myocardium by 12 weeks. Once established, six pigs were given daily dietary CoQ10 for 30 days, while the remaining six swine were given normal chow. Cardiac function was assessed by ECHO, and expression of mitochondrial proteins were analyzed by Western blot. RESULTS: Cardiac function as measured by regional wall thickening did not improve in hibernating regions (41.31 ± 5.13) as compared to an internal, non-ischemic control (72.47 ± 7.24) under inotropic stimulation. Measurement of Electron Transport Chain proteins by western blot revealed increased expression following CoQ10 administration as compared to hibernation alone. Complexes 2 (0.052 ± 0.01 vs. 0.11 ± 0.09) and 5 (2.03 ± 0.73 vs. 7.59 ± 2.17) were significantly increased ($p = 0.03$; $p = 0.01$) CONCLUSION: Dietary supplementation with CoQ10 increases expression of electron transport chain proteins that are suppressed in hibernating myocardium. Although the increase in electron transport chain proteins does not lead to an improvement in basal regional function, we speculate that this up-regulation in ETC proteins might enhance energetics at high work states in the long-term and mitigate the development of heart failure.

Research Topic: Heart Disease

11. Melanoma Treated with Mohs Micrographic Surgery Using a Modified 15-Minute MART-1 Immunostain: Discussion of Technique and Experience

Cheraghi, Nikoo [1]; Demer, Addison [1]; Meister, Andrew [2]; Lee, Peter [1,2]

1. University of Minnesota
2. Park Nicollet

Abstract: Background: Mohs micrographic surgery (MMS) is increasingly utilized for the treatment of melanoma *in situ* (MIS) and invasive melanoma. The process of performing MMS using immunohistochemistry (IHC) can be tedious and time-consuming, therefore, limiting the number of melanomas that can be treated per MMS session. Anecdotally, the standard 10-minute MART-1 immunostains are challenging to replicate reliably. Purpose: We describe a novel method of tissue processing and staining for cutaneous melanomas treated with MMS. This modified 15-minute MART-1 IHC protocol allows for ease of use, efficiency, and reliability. We also describe the characteristics of melanomas that have been treated with this method thus far at our institution. Protocol: A Wood's lamp is used to determine the extent of the melanoma. Depending on whether the lesion is MIS or invasive melanoma, the tissue is processed in a specific manner with a positive control. The first stage is taken as a 2-mm margin around the debulk. Tissue cuts are stained in alternating fashion with either hematoxylin and eosin (H&E) or MART-1 using our 15-minute MART-1 IHC protocol. Methods: A retrospective chart review was performed including all MIS and invasive melanomas treated with MMS with MART-1 immunostain by a single surgeon from October 2016 to November 2017. Data was collected on subject characteristics including subject age and gender, melanoma depth, number of stages needed to clear the melanoma, pre-operative and post-operative sizes, and whether the melanoma was primary, incompletely excised, or recurrent. Results: Over fourteen months, 155 melanomas (111 *in situ*) were treated with this protocol. Sixty six percent of subjects were male with an average age of 68.8 years. The melanomas were mostly primary tumors (85%) located on the head and neck (88%). On average, it took 1.39 stages to clear the melanomas. Conclusion: MMS using a 15-minute MART-1 stain can be used to treat a wide variety of melanoma types and is easy to use. We describe a standardized and reliable method of staining using a modified 15-minute MART-1 immunostain.

12. Linking Connectomics to Biochemistry of Aging

Crocker, Jillian [1]; McCarten, J. Riley [2,3]; Terpstra, Melissa [1,4]; Hagy, Hannah [1]; Marjanska, Malgorzata [1,4]; Hemmy, Laura [2,5]; Mangia, Silvia [1,4]

1. Center for Magnetic Resonance Research, University of Minnesota
2. Geriatric Research, Education and Clinical Center, Minneapolis VA Health Care System
3. Department of Neurology, University of Minnesota
4. Department of Radiology, University of Minnesota
5. Department of Psychiatry, University of Minnesota

Abstract: The Human Connectome Project on Aging (HCPA) is a cross-sectional, multi-center study funded by the National Institutes of Health (NIH) that uses magnetic resonance imaging (MRI) to map brain connectivity in typically aging adults. The study aims to enroll 1,200 individuals nationwide aged 36 years and older to collect data across the adult lifespan. The University of Minnesota (UMN) Center for Magnetic Resonance Research (CMRR) is one of four HCPA acquisition sites and has enrolled over 170 participants. In addition to MRI, HCPA acquires several behavioral and cognitive measures including the Montreal Cognitive Assessment (MoCA), NIH Toolbox, the Rey Auditory Verbal Learning Test (RAVLT) short version, and the Trail Making Tests (TMT). In 2017, the NIH funded a University of Minnesota CMRR study to measure neurochemistry by adding noninvasive magnetic resonance spectroscopy (MRS). The addition of this data makes it possible to noninvasively quantify concentrations of neurochemicals in the brain and compare it to brain connectomics. The areas of interest to be studied include the posterior cingulate cortex (PCC) and frontal cortex (FC). Individuals who successfully complete the HCPA at the University of Minnesota may be eligible to participate if they score above a 23 on the MoCA. The eligibility requirements for participants between the ages of 60 to 89 includes a comprehensive neuropsychological and neurological evaluation to shift the study focus to healthy aging rather than typical aging. Additionally, amyloid positron emission tomography (PET) data will be collected on individuals over 60 years of age to distinguish differences between cognitively healthy aging and apparent healthy aging with positive amyloid PET. This project is collaborating with the Minnesota Alzheimer's Connectome Partnership (MACP), who will be enrolling clinically normal individuals, patients with Alzheimer's Disease, and patients with mild cognitive impairment, all of whom will complete phenotyping and HCPA style imaging. The MACP individuals will also complete the MRS imaging protocol to ultimately examine the underlying mechanisms that influence the shift from healthy brain aging to neurodegeneration.

13. **Improving Inpatient Diabetes Care by Reducing Bedside Glucose Monitoring and Optimizing Correctional Insulin Dosing for Low Risk Patients with Type II Diabetes**

Davis, Emily [1]; Selvey, Paige [1]; Deshpande, Aakash [1]; James, Adam [1]; Ercan-Fang, Nacide [2]; Wilt, Tim [2]; Drake, Tyler [2]; Duan-Porter, Wei [2]; Ingraham, Kay [1,2]; Beard, Albertine [2]

1.   University of Minnesota Medical School
2.   Minneapolis VA Health Care System

Abstract: Patients with type 2 diabetes (T2DM) treated with outpatient diet or oral hypoglycemic agents are frequently exposed to intensive blood glucose monitoring and subsequent insulin correction for modestly elevated glucose values when admitted to the hospital for noncritical illnesses. This results in laboratory and medication costs, resource utilization, and patient discomfort without demonstrated health benefits or improvements in long-term glycemic control. While recommendations exist for glucose monitoring frequency and control among critically ill patients, evidence is lacking for general ward patients. Our aim is to improve the value of health care delivered for hospitalized adults with low risk T2DM defined as those receiving outpatient diet or oral hypoglycemic therapy and hospitalized for noncritical illnesses. Using a Continuous Quality Improvement approach we developed a threefold strategy involving nursing, pharmacist, and physician education and alteration of the standardized T2DM order set for patients with 'low risk T2DM' to: (1) reduce bedside glucose monitoring intensity; (2) eliminate single unit insulin correction dosing; (3) raise insulin correction dosing initiation threshold to a glucose of > 220. Our main outcomes were: 1) total number of glucose monitoring tests per hospital admission; 2) total number of administered doses of correctional insulin per hospitalized patient; 3) serious hypo or hyperglycemic events.

Research Topic: Diabetes & Major Complications
Funding agencies: N/A
Grant support: N/A

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14. **Energy Return in Prosthetic Feet for High Activity Users During Weighted and Unweighted Walking**

Dellamano, Clifford [1,2]; Ray, Samuel [3]; Schnall, Barri [3]; Hendershot, Brad [3]; Koehler-McNicholas, Sara [1]; Hansen, Andrew [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota
3.   Walter Reed National Military Medical Center

Abstract: Many Service members and Veterans with lower-limb amputations, as well as other populations of highly active prosthesis users, have the potential and desire to resume physically demanding occupations requiring the carriage of heavy loads (e.g., military service, firefighters, farmers, ranchers, construction workers). The category of lower-limb ankle-foot systems known as energy storage and return (ESAR) prostheses are the standard of care for these highly active users. However, data comparing currently available ESAR prostheses are limited in availability and scope. Thus, it is currently unknown which prosthetic ankle-foot systems are best designed to accommodate heavy load carriage while also providing good overall function and mobility during unweighted activities. This information could be highly valuable to clinicians, as it may assist in the prescription of prosthetic feet to maximize patient outcomes. The main objective of this study was to analyze the behavior of a subset of commercially available prostheses to determine their late-stance energy return capabilities under weighted and unweighted walking conditions. Quantitative gait analysis was performed on three users with unilateral, transtibial amputation, in which a unified deformable (UD) segment model was applied to calculate power done by the prosthesis during standard gait. Power was then integrated between zero crossings to determine total late-stance energy return of the prosthetic forefoot keel structure. Results from this analysis indicated that while energy return during late stance did not vary considerably between weighted and unweighted conditions for any of the prostheses tested, a wide range of energy return capabilities was present across prostheses. Comparison of these data with forefoot stiffness data showed that more compliant forefoot keel structures appeared to provide more late-stance energy return compared to feet with stiffer forefoot keel structures. These results suggest that prosthetic ankle-foot systems with more compliant forefoot keel structures may be better suited to accommodate users whose high activity involves the carriage of added loads, but further research is necessary to explore the prostheses on the ends of this spectrum.

Research Topic: Special Populations
Funding agencies: DOD
Grant support: This work was supported by the BADER Consortium via the Congressionally Designated Medical Research Program (Award # W81XWH-11-2-0222).

15. **Investigation at a Veterans Affairs Medical Center (VAMC) of Spurious Legionella Environmental Testing Results and High Lab-to-Lab Variability among Four Commercial Laboratories**

DeVries, Aaron [1]; Merideth, Daniel [1]; Holter, John [1]; Harper, Jane [1]; Clabots, Connie [1]; Van Schyndel, Ryan [1]; Crossley, Kent [1]; Johnson, James R. [1]

1.   Minneapolis VA Health Care System

Abstract: Background: The Department of Veterans Affairs (VA) requires quarterly water Legionella environmental testing (LET). The Minneapolis VA Medical Center (MVAMC) began LET in 2008. All results were neg. until 11/2015, when a new (CDC ELITE-certified) LET lab (lab1) reported Legionella spp. (Lsp) in 12/40 (30%) MVAMC samples. Healthcare-associated legionellosis (HAL) and LET reliability were investigated. Methods: Records of all 2015 MVAMC Lsp cases and potentially exposed patients were reviewed. In 1/2016, test and control water samples were sent to 4 contract LET labs. MVAMC water samples were collected from 5 purportedly Lsp-pos. sites. A sterilized-water neg. control and 3 pos. controls (10x dilutions of L. pnueumophila type 1 [Lp1] stock culture) were created. Each LET lab received 18 masked samples: 1 neg. control, 3 pos. controls, and 5 test samples, all in duplicate. Purported Lsp isolates underwent mass spectrometry (MALDI-TOF). Results: During intensified LET (11/6/15-1/11/16), Lab1 ostensibly found Lsp in 77 (26%) of 296 MVAMC water samples. Mitigation and remediation was performed. No HAL cases were identified. The 4 LET labs' blinded test results (cfu/mL) were as shown (Table 1). In 2/2016 Lab3 tested all sites that Lab1 had reported as Lsp-pos., including areas not remediated; all were neg. for Lsp. By MALDI-TOF, all 18 purported MVAMC Lsp isolates from Lab1 were diverse non-Lsp environmental organisms. After learning of these results, Lab1 withdrew from its LET contract. CDC and VA experts were notified. Conclusions: A (CDC-certified) LET lab provided spurious results, with enormous consequent costs to MVAMC. Lab-to-lab differences were found between the remaining 3 labs, raising concern about accuracy for both pos. and neg. LET results. Healthcare systems must be cautious in deciding when to perform LET and how to interpret the results.

Research Topic: Infectious Diseases
Funding agencies: N/A
Grant support: N/A

16. **Precision Medicine in Mental Health Care (PRIME Care)**

Dieperink, Eric [1]; Uphoff, Lara [1]

1.   Minneapolis VA Health Care System

Abstract: Background: In the last several years, commercial pharmacogenetic (PGx) testing for the selection of psychotropic medications has become widespread as a means of implementing 'precision medicine', with some insurers electing to cover the cost of testing. These developments have put increasing pressure on the Veterans Health Administration to implement a mental health focused PGxs program, especially for treating depression, but without sufficient scientific study to support the utility of its clinical application. Objectives: This project is designed to evaluate the utility of PGx testing in treating Major Depressive Disorder. Methods: The project is a multi-site randomized clinical trial in which 2000 patient/provider dyads will be randomly assigned to receive the results of the PGx battery right after randomization (i.e., the intervention group) or after 6 months of treatment as usual (i.e., the delayed results group). The study will test the following primary hypotheses: 1. Veterans with major depressive disorder (MDD) whose care is guided by the results of the PGx battery (the intervention group) will have a higher rate of remission of depression than those in the delayed results group. 2. Provider/patient dyads in the intervention group will use fewer contraindicated medications or doses of medication based on established PGx criteria than the delayed results group. The patient inclusion and exclusion criteria are designed to target a population of patients with a major depression diagnosis who are starting or switching antidepressants. Anticipated Impact on Veteran's Healthcare: Despite the high prevalence of depression and its adverse impact on healthcare costs and life functioning, its treatment is often inadequate. As shown in several studies, to achieve remission from depression, patients and providers must be persistent and try multiple treatments until they find one that is both tolerable and effective. However, with each round of treatment, there is greater attrition from care. Replication of the results of the few PGx implementation studies that have been conducted to date suggest that PGx could enhance the treatment of MDD and provide an impetus for early diagnosis and treatment initiation, resulting in more rapid and higher rates of remission.

Research Topic: Mental Illness
Funding agencies: HSR&D
Grant support: PRIME Care PRecision Medicine in MEntal Health Care HSR&D SDR 16-348

17. **The Health Practices Inventory: Patterns of conventional and complementary non-pharmacological therapy use by Veterans**

Donaldson, Melvin [1]; Polusny, Melissa [1]; MacLehose, Rich [2]; Goldsmith, Elizabeth [1]; Hagel Campbell, Emily [1]; Miron, Lynsey [1]; Thuras, Paul [1]; Krebs, Erin [1]

1.   Center for Care Delivery & Outcomes Research, Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Background A growing body of research examines complementary and integrative health approaches in pain management, but heterogeneity of specific modalities included in prior studies challenges the external validity of findings. Objectives The goal of the current study was to describe the development of the Pain Management Inventory and to identify latent classes of users of non-pharmacological health approaches among U.S. Veterans of the recent wars in Iraq and Afghanistan. Research Design Latent Class Analysis; observational study Methods A new self-report instrument, the Health Practices Inventory (HPI), was developed to assess use of 19 common conventional and complementary non-pharmacological health approaches. National Guard Veterans from a longitudinal cohort (n = 3,843) were invited to participate in a follow-up mailed survey, including the HPI. We classified each HPI approach into complementary versus conventional and active versus practitioner-delivered. We used latent class analysis to identify distinct latent classes of users of non-pharmacological health approaches. Probability of membership in each class was calculated and respondents were assigned to the maximum-likelihood class based on their PMI responses. Results Of 3,843 cohort members contacted, 1,850 (48.1%) responded. Among all respondents, 74% endorsed use of any HPI approach. The best fit model had 6 classes: Low users (47% of respondents), Exercise users (24%), Psychotherapy users (5%), Chiropractic & massage users (14%), Mindfulness & relaxation users (5%), and Multimodal high users (4%). Patient demographics, chronic pain, mental health, and substance use varied by class. Conclusions These findings support the existence of six user subgroups characterized by use of multiple non-pharmacological health approaches. More than one-fourth of respondents reported using multiple complementary modalities over the previous year. Patterns and predictors of Veterans use of non-pharmacological therapies for their health differs between these classes. Future studies are needed to examine the generalizability of these latent classes in other patient populations.

18. **Hospitalization and Change in Gait Speed and Risk of New Mobility and Functional Limitations Among Older Adults. The Health ABC Cohort Study.**

Duan-Porter, Wei [1,2]; Vo, Tien [2]; Ullman, Kristen [1]; Langsetmo, Lisa [2]; Strotmeyer, Elsa [3]; Taylor, Brent [1]; Santanasto, Adam [3]; Cawthon, Peggy [4]; Newman, Anne [3]; Simonsick, Eleanor [5]

1.   Center for Care Delivery & Outcomes Research, Minneapolis VA Health Care System
2.   University of Minnesota
3.   University of Pittsburg
4.   California Pacific Medical Center
5.   National Institute of Aging

Abstract: Background: How hospitalization impacts physical performance and self-reported mobility limitations is unclear. Objective: Determine associations of hospitalization with gait speed change and likelihood of new limitations in mobility and activities of daily living (ADLs). Design: Prospective cohort study. Setting: 2 US sites Participants: 2,963 black and white, community-dwelling adults, aged 70-79 years at baseline, no difficulty in mobility and ADLs prior to hospitalization. Measurements: Annually assessed gait speed, self-reported limitations in mobility (walking º mile and climbing 10 steps) and ADLs (transferring, bathing, dressing, and eating). Gait speed change standardized using standard deviation at baseline. Generalized estimating equations examined associations of hospitalizations within 1-year intervals with concurrent annual gait speed change and odds of new limitations. Results: After accounting for demographics, past hospitalization, health conditions, symptoms, and health-related behaviors, any hospitalization was associated with small decrease in gait speed (standardized effect -0.24 [95% CI -0.31, -0.18], absolute change -0.05 m/s [CI -0.06, -0.04]), and higher odds of new limitations in mobility or ADLs (odds ratio [OR] 1.97 [CI 1.70, 2.28]). Multiple hospitalizations within a year were associated with larger gait speed decline (standardized effect -0.40 [CI -0.54, -0.27], absolute change -0.09 m/s [CI -0.12, -0.06]), and higher odds of new limitations in mobility or ADLs (OR 2.96 [CI 2.23, 3.95]). Hospitalizations were also associated with higher odds of new limitations in mobility and ADLs, when analyzed as separate outcomes. Limitations: Missing gait speed assessments after hospitalization may have biased associations towards the null. Conclusion: For functionally independent older adults, hospitalizations were associated with small to moderate declines in gait speed and increased likelihood of new limitations in mobility and ADLs. Intervention studies to mitigate hospitalization-associated declines in mobility yare needed. Funding source: none

19. Evidence Review–Social Determinants of Health for Veterans

Duan-Porter, Wei [1,2]; Martinson, Brian [1,3,4]; Greer, Nancy [1]; Taylor, Brent C [1,2,4]; Ullman, Kristen [1]; McKenzie, Lauren [1]; Rosebush, Christina [1]; MacDonald, Roderick [1]; Falde, Samuel [2]; Wilt, Timothy J [1,2]

1.   Minneapolis VA Health Care System, Center for Care Delivery & Outcomes Research
2.   University of Minnesota Medical School
3.   HealthPartners Institute
4.   University of Minnesota School of Public Health

Abstract: Background: Veterans Health Administration is committed to providing high quality care and addressing health disparities for vulnerable Veterans, but VA policymakers need guidance on how to address social determinants in operations planning, and day-to-day clinical care for Veterans. Methods: MEDLINE (OVID), CINAHL, PsycINFO, and Sociological Abstracts were searched up to January 2017. Additional articles were suggested by peer reviewers and/or found through search of work associated with US and VA cohorts. Eligible articles compared Veterans vs non-Veterans, and/or Veterans engaged with those not engaged in VA healthcare. Our evidence maps summarized study characteristics, social determinant(s) addressed, and whether health behaviors, health services utilization, and/or health outcomes were examined. Qualitative syntheses and quality assessment were performed for articles on rurality, trauma exposure, and sexual orientation. Results: We screened 7,242 citations and found 131 eligible articles–99 compared Veterans vs non-Veterans, and 40 included engaged vs non-engaged Veterans. Most articles were cross-sectional and addressed socioeconomic factors (e.g., education and income). Fewer articles addressed rurality (n = 20), trauma exposure (n = 17), or sexual orientation (n = 2); none examined gender identity. We found no differences in rural residence between Veterans and non-Veterans, nor between engaged and non-engaged Veterans (moderate strength evidence). There was insufficient evidence for role of rurality in health behaviors, health services utilization, or health outcomes. Trauma exposures, including from events preceding military service, were more prevalent for Veterans vs non-Veterans and for engaged vs non-engaged Veterans (low strength evidence); exposures were associated with smoking (low strength evidence). Discussion: Little published literature exist for some emerging social determinants. We found no differences in rural residence between our groups of interest, but trauma exposure was higher in Veterans (vs non-Veterans) and engaged (vs non-engaged). We recommend consistent measures for social determinants, clear conceptual frameworks, and analytic strategies that account for the complex relationships between social determinants and health.

20. A pilot examination of mHealth approaches for improving sleep among National Guard soldiers

Erbes, Christopher [1-3]; Hansen, Lucas [4]; Koffel, Erin [1-3]; Polusny, Melissa [1-3]; Ferguson, John [1-2]; Schmer-Galunder, Sonja [5]

1. Minneapolis VA Health Care System
2. University of Minnesota
3. Center for Care Delivery & Outcomes Research
4. University of St. Thomas
5. Smart Information Flow Technologies

Abstract: Background. This study compared two mHealth (smartphone) applications for enhancing sleep hygiene and addressing sleep problems among National Guard soldiers. Performance Triad (PT) uses a traditional educational approach with informative slides presented to the user on their phone screen. MORA presents sleep education through interactive game play in which a player's choices regarding sleep behaviors during the game affect gameplay and success. The MORA app accesses data on real world behaviors (such as step count for exercise and sleep activity) from the user's smartphone to further affect game play and provide feedback to the user. We compared 1) app satisfaction and utilization, and 2) changes in sleep hygiene knowledge, behaviors and problems between soldiers using the 2 apps. Methods. A group of 83 participants were randomly assigned to use either the PT app (n = 43) or the MORA app (n = 40) over the course of 4 weeks. In addition to MORA or PT, additional sleep tracking and reminder apps were downloaded to enhance the functionality of MORA and facilitate data collection. Participants in both conditions downloaded the same set of additional apps. Participants completed measures evaluating their satisfaction with the apps and app usage (the System Usability Scale) on a weekly basis and measures of sleep knowledge (the Sleep Beliefs Scale), behaviors (the Sleep Hygiene Index) and outcomes (the Insomnia Severity Index) at baseline, post-treatment (Week 4), and 2 months following treatment. A subset of participants completed brief telephone interviews to further assess their use and impressions of the app. Results. No significant differences were found on app usage or satisfaction. There were no differences between groups on sleep hygiene knowledge or behavior. While both groups showed significant decline in sleep related problems over time, the two groups did not differ on their rate of reduction. Post-treatment interviews suggested that some users struggled with the MORA game (finding it too simple or too complicated) and that the sleep tracking app was sometimes perceived as being more salient and helpful (rather than MORA or PT). Conclusions. mHealth approaches show promise in improving sleep with this population. However, future studies of novel sleep hygiene training must attend to the interests and gaming practices of the target audience as well as the role of more general behavior tracking apps in altering behaviors and outcomes.

21. Success Factors and Barriers in Lung Cancer Screening Program Implementation in the VA: Results of a Qualitative Study

Fabbrini, Angela [1]; Lillie, Sarah [1]; Fu, Steven [1,2]; Wendt, Christine [1,2]; Melzer, Anne [1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Purpose/Objectives: Lung cancer screening (LCS) is a recent clinical innovation that, if implemented correctly, decreases mortality from lung cancer through early detection. LCS is complex, which may create barriers to implementation. The structure and size of LCS programs varies depending on the size and needs of each site. We sought to formally assess the needs and perceived barriers of programs considering formal implementation, informed by the experiences of sites that are currently screening. Methods: We identified five VA sites currently performing lung cancer screening and five sites that were considering LCS program implementation. We identified six elements from the Consolidated Framework for Implementation Research hypothesized to be key for LCS implementation: implementation climate, relative priority, leadership engagement, knowledge and beliefs, formally appointed leaders, and available resources. These elements were developed into two interview guides administered by phone to one contact at each location. Results: Ten providers were contacted. Several themes emerged from the interviews: for all sites interviewed, the most important elements identified for starting and maintaining a program were leadership support, formally identified program staff, and access to medical informaticists. For existing programs, three sites employed a coordinator to assist with the implementation and administration of an LCS program. Many sites felt knowledge of LCS among primary care and leadership was low, with relatively low program implementation prioritization. Most sites felt that primary care would be open to providing LCS if it would not add significantly to workload. Among sites considering LCS, several additional barriers were identified, these included: i) variable and contract staffing in radiology resulted in lack of guideline adherent impressions to guide follow up recommendations, ii) smaller sites had limited subspecialty staff to provide oversight and expertise in the management of small nodules, and iii) concerns that increasing the number of moderate risk nodules would tax limited consultative resources. Conclusion: Defined program leadership, strong institutional support, dedicated FTE, and access to informatics support were perceived as success factors. Perceived barriers to formal screening programs included lack of standardized radiology reports, limited specialty care resources, and low institutional knowledge and priority.

Research Topic: Health Systems
Funding agencies: N/A

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22. Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia

Fink, Howard A [1,2]; Butler, Mary [2]; Brassure, Michelle [2]; Davila, Heather [2]; Desai, Priyanka [2]; McCarten, J. Riley [1,2]; Hemmy, Laura [1,2]; Ratner, Edward [1,2]; McCreedy, Ellen [2]; Barclay, Terry [3]

1. Minneapolis VA Health Care System
2. University of Minnesota
3. HealthPartners

Abstract: Objective. To assess evidence for interventions aimed at preventing or delaying the onset of age-related cognitive decline, mild cognitive impairment (MCI), or clinical Alzheimer's-type dementia (CATD). Methods: We searched Ovid Medline®, Ovid PsycINFO®, Ovid Embase®, and Cochrane Central Register of Controlled Trials (CENTRAL) bibliographic databases, and did hand searches of references of prior reviews, eligible studies, gray literature and expert recommendations for randomized and nonrandomized controlled and quasi-experimental observational trials. We extracted data, assessed risk of bias, summarized results for studies without high risk of bias, and evaluated strength of evidence for studies with sufficient sample size. Cognitive outcomes were grouped into domains to facilitate analysis; strength of evidence was assessed by MCI or CATD incidence and cognitive outcome domain. Results: We identified 263 eligible studies addressing 13 classes of interventions: cognitive training, physical activity, nutraceuticals, diet, multimodal interventions, hormone therapy, vitamins, antihypertensive treatment, lipid lowering treatment, nonsteroidal anti-inflammatory drugs (NSAIDs), antidementia drugs, diabetes treatment, and 'other interventions.' We found no high-strength evidence for any intervention and mostly low-strength evidence that a wide variety of interventions had little to no benefit for preventing or delaying age-related cognitive decline, MCI, or CATD. Conclusions: Methodological problems in the available literature were widespread. Consistent cognitive outcomes, longer followups, and addressing attrition is necessary. More work is needed to understand the relationship between intermediate outcomes such as cognitive test results and the onset of MCI and CATD. Testing interventions that address modifiable risk factors can help to establish their causative role in cognitive decline.

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: N/A

23. Comparing Depressive Symptom Assessment Approaches in the Context of PTSD

Fleming, Cassandra [1]; Hollowell, Christopher [1,2]; Pokorny, Victor [1,2]; Keacher, Lisa [1]; Davenport, Nicholas [1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Introduction: Posttraumatic stress disorder (PTSD) is a highly heterogeneous and complex disorder, with 27 possible combinations of various symptoms that lead to qualification of the diagnosis. In a study of OEF/OIF Veterans, we attempted to examine depressive features of PTSD and compare them across three assessment approaches in order to observe differences in symptom reporting. To that end, we examined the relationships of five depressive symptoms across measures of PTSD and depression in the context of PTSD. Methods: Bivariate correlations were conducted to observe relationships between the sum of 5 depressive symptoms of the PTSD Checklist (PCL), the Clinician-Administered PTSD Scale (CAPS), and the Beck Depression Inventory (BDI). Split file correlations were then conducted to account for the presence of Lifetime PTSD, in order to better differentiate depressive items across diagnoses within each PTSD measure. Results: The PCL and BDI depressive sub scores correlated highly; the CAPS and BDI sub scores showed a low correlation. No PTSD: Moderate rates of depressive symptoms were seen in the PCL while low rates were seen in the CAPS. PTSD: Moderate rates of depressive symptoms were seen in the PCL while no relationship was seen in the CAPS Overall: there were poor correspondences between similar, individual items across all assessments. Therefore, little differentiation between depressive symptoms and PTSD could be observed. Conclusion: The results further demonstrated the lack of reliability between the CAPS and the PCL. While major differences exist between PTSD measures, little differentiation in depressive symptoms was observed in the context of PTSD prevalence. Furthermore, the rates of depressive symptoms across PTSD prevalence conflict across PTSD measures. Further comparisons to a clinician-administered depression scale are needed to validate these findings.

24. VA CSP #578: Prevention of Serious Adverse Events Following Angiography (PRESERVE)

Garcia, Santiago [1]; McFalls, Edward [1]; Vakil, Kairav [1]; Herrmann, Rebekah [1]; Nguyen, Jennifer [1]; Kantorowicz, Alexandria [1]; DeCarolis, Douglas [1]; Tacy, Meyeraan [1]; Weisbord, Steven [2]; Palevsky, Paul [2]

1. Minneapolis VA Health Care System
2. VA Pittsburgh Healthcare System

Abstract: During angiography, contrast dye is used to visualize the arteries in x-rays. Though this contrast is necessary for the procedure, patients with poor kidney function are at an increased risk for developing contrast-induced acute kidney injuries (CIAKI). This damage can result in the accelerated progression of underlying chronic kidney disease (CKD), need for dialysis, death, and substantial increases in health care costs. To prevent this complication, the standard intervention before angiography has been intravenous isotonic sodium chloride. While other studies have compared its efficacy to intravenous sodium bicarbonate and oral acetylcysteine, results have been inconsistent and inconclusive. Therefore, PRESERVE was developed to identify the safest and most effective clinical treatment that protects renal function in patients with CKD who undergo angiography procedures and receive arterial contrast. PRESERVE was a double-blind, placebo and comparator-drug-controlled, randomized multi-site clinical trial comparing two IV fluids and oral acetylcysteine vs placebo capsules in their effectiveness in preventing CIAKI in Veterans with established CKD undergoing angiography. Follow-up included collecting blood samples, phone calls, and reviewing medical records at 3-5 days and 90-104 days post-procedure to determine primary and secondary endpoints. The primary endpoint was a composite of death, need for dialysis, or a persistent increase of at least 50% in serum creatinine from baseline at 90-104 days. Secondary endpoints were CIAKI at 3-5 days after baseline, death within 90 days, and hospitalization within 90 days. There were no significant between-group differences (IV sodium bicarbonate vs. IV sodium chloride; oral acetylcysteine vs. placebo) in the rates of CIAKI. There was no benefit of IV sodium bicarbonate over IV sodium chloride, or of oral acetylcysteine over placebo, in preventing renal complications (death, need for dialysis, persistent decline of kidney function at 90 days, or contrast-associated acute kidney injury) in patients at high risk for renal complications undergoing angiography. (The study was funded by the U.S. Department of Veterans Affairs Office of Research and Development Cooperative Studies Program and the National Health and Medical Research Council of Australia; PRESERVE ClinicalTrials.gov number, NCT01467466.)

25. Identifying Predictors of Clinical Response in Medication Refractory Depression with Comorbid Mild Traumatic Brain Injury to Deep Transcranial Magnetic Stimulation

Gentz, Carolyn [1]; Albott, Sophia [2,3]; Fenske, Alicia [2]; Branson, Mariah [2]; Lim, Kelvin [1-3]

1. Defense and Veterans Brain Injury Center
2. Minneapolis VA Health Care System
3. University of Minnesota

Abstract: Background: Traumatic brain injury (TBI) is a common problem with 1.5 million new injuries in the United States each year. In the military, over 25,000 TBIs were reported in 2014 with 84% classified as mild (mTBI). Depression is present in as many as 50% of mTBI cases. Unfortunately, those with mTBI that develop psychiatric complications have overall poorer outcomes. Patients with mTBI and depression typically get management in line with their non-mTBI depressed counterparts. These interventions have varying degrees of success. In the general population, approximately 80% of people treated for depression respond to medications. In mTBI, success rates are much lower (Ashman et al., 2009) with increased side effects. Ultimately, many mTBI patients require psychostimulants to improve mood and cognitive symptoms and many mTBI depressed patients experience severe medication refractory depression (MRD). Deep Transcranial Magnetic Stimulation (dTMS) has shown tremendous promise in MRD, but it has yet been evaluated in comorbid mTBI and depression. Methods: This study is an open-label clinical trial. Participants will complete 20-37 dTMS treatments based on response to treatment and three follow-up visits (1, 3, and 6 months). Results: To date, four subjects have received treatment. The subjects tolerated the treatments well and experienced a reduction in symptom severity. Conclusions: Initial results are promising with good clinical response. The study is continuing to recruit with a target of 60.

Research Topic: Mental Illness
Funding agencies: N/A
Grant support: N/A

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26. Transcranial Direct Current Stimulation (tDCS) Paired with a Cognitive Task Reduces Impulsivity in a Clinical Population of Veterans

Gilmore, Casey [1,2]; Carson, Molly [1,2]; Du, Connie [1,2]; Branson, Mariah [1,2]; Lim, Kelvin [1-3]

1. Defense and Veterans Brain Injury Center
2. Minneapolis VA Health Care System
3. University of Minnesota

Abstract: Impulsivity is a multidimensional personality trait observed across a variety of psychiatric disorders. Transcranial direct current stimulation (tDCS) applied over dorsolateral prefrontal cortex (DLPFC) has shown promise as an intervention to reduce impulsivity. This was a randomized, single-blind, sham-controlled study to investigate the effects of tDCS paired with a decision-making task on risk-taking in Veterans with a clinical history of impulsive behavior. Participants performed the Balloon Analogue Risk Task (BART) while concurrently receiving either active or sham tDCS (right anodal/left cathodal over DLPFC) twice a day for five days. To evaluate generalization, the Risk Task was performed before and after the complete course of intervention. To evaluate durability, the BART and Risk Task were administered again at one and two month follow-up sessions. Fifteen Veterans received active tDCS and 15 received sham tDCS. For the trained BART task, growth curve analysis (GCA) examining variation of the growth rates over time showed no significant variations in individual trajectory changes. For the untrained Risk Task, GCA showed that the active tDCS group had a significant 46% decrease in risky choice from pre- to post-intervention, which persisted through the one and two month follow-up sessions. The sham tDCS group showed no significant change in risky choice from pre- to post-intervention. tDCS over DLPFC paired with a decision-making task effectively reduced risk-taking behavior in a group of Veterans with clinically-relevant impulsivity. Results suggest that this approach may be an effective neuroplasticity-based intervention for patients affected by impulsivity.

Research Topic: Mental Illness
Funding agencies: N/A
Grant support: Defense and Veterans Brain Injury Center (DVBIC)

27. **Symptom validity screening and mild traumatic brain injury in a non-treatment seeking Veteran sample**

Gilmore, Casey [1,2]; Lamberty, Greg [2,3]; Nelson, Nathaniel [4]; Lim, Kelvin [1-3]

1.   Defense and Veterans Brain Injury Center
2.   Minneapolis VA Health Care System
3.   University of Minnesota
4.   University of St. Thomas

Abstract: Assessment of symptom validity in Veterans with a history of traumatic brain injury (TBI) is often completed in clinical neuropsychological evaluations, as an accurate assessment of TBI characteristics is critical for diagnosis and treatment. Outside of the clinical context, such as in a research study, it is still important to assess symptom validity, but studies have not approached this in a uniform manner and may be reluctant to add time to protocols to do so. In this study, Veterans with a reported history of mild TBI were compared with those that reported no TBI history (controls). Two measures that have been developed in the context of assessing validity of symptom reporting in Veterans are the Mild Brain Injury Atypical Symptoms Scale (mBIAS) and the Validity-10 Scale of the Neurobehavioral Symptom Inventory. Mild TBI presence and severity was assessed via consensus review of responses to the Minnesota Blast Exposure Screening Tool (MN-BEST) semi-structured interview. Veterans with mTBI (n = 79) had significantly elevated scores on both the mBIAS (t= 3.0, p=.003) and Validity-10 (t= 4.8, p<.001) compared to controls (n = 83). Notably, scores on the mBIAS and Validity-10 were strongly correlated with traditional validity measures from the MMPI-2-RF, as well as with mTBI severity scores from the MN-BEST. Veterans with a history of mTBI had a tendency to report a higher level of symptoms than did Veterans without mTBI, and greater symptom reporting was associated with greater mTBI severity. Importantly, while mBIAS and Validity-10 scores were higher in the mTBI sample, scores were not in a range that would be considered clinically elevated. Results suggest that the mBIAS and Validity-10 are useful measures of symptom validity in non-treatment seeking Veterans.

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28. **Improving the Delivery of Inpatient Tobacco Cessation Treatment for Hospitalized Smokers**

Glowacki, Alison [1]; Anderson, Travis [1]; Fairbairn, Elizabeth [1]; MacDonald, David [2]; Melzer, Anne [2]

1.   University of Minnesota
2.   Minneapolis VA Health Care System

Abstract: Background: Research has identified that providing tobacco cessation medications during hospitalization improves patient comfort by reducing nicotine withdrawal symptoms and improves quit rates following hospitalization. However, the MAHCS has an inefficient process for providing tobacco cessation medications and counseling to patients, causing frustration among staff and patients. MVA Health Care System has been meeting the Joint Commission Inpatient Tobacco Measures with reasonable success, yet there was frustration with the process. Objective: To create an efficient and patient-centered process for tobacco cessation treatment for inpatient smokers. Methods: A team involving pharmacists, physicians, nurses, informaticists, and administrators was brought together to evaluate the process and perform iterative assessments to identify novel solutions through process mapping, interviewing team members, and data gathering, Results: We identified many redundant steps and inefficiencies. To create a streamlined process that is patient focused, we specifically aimed to: 1) Reduce the number of times charts are accessed by 25% from a current state of 10 per patient. 2) Increase the proportion of smokers receiving nicotine replacement therapy (NRT) from 25% to 50% on admission and from 10% to 20% on discharge. 3) Increase the rate of appropriate outpatient smoking cessation consults from 43% to 85%. A gap analysis revealed the following: a fragmented process, a focus on acute illness, and poor timing of certain orders. The solutions include pharmacists counseling on tobacco cessation, prescribing NRTs, and offering outpatient tobacco cessation counseling on discharge. Currently, a working group within the Pharmacy Service Line is in the process of developing a pilot project to implement and evaluate the effect of these proposed solutions. The pilot project is planned for implementation in the summer of 2018. Implications: Improving this process required multidisciplinary collaboration. Centralizing process ownership in one discipline–pharmacy–will allow for novel methods of ensuring high quality care.

29. Chronic Musculoskeletal Pain Measures: A Focused Evidence Review

Goldsmith, Elizabeth S [1,2]; Taylor, Brent [1,2]; Greer, Nancy [1]; Murdoch, Maureen [1,2]; MacDonald, Roderick [1]; McKenzie, Lauren [1]; Rosebush, Christina [1]; Wilt, Timothy J [1,2]

1.   Minneapolis VA Health Care System, Center for Care Delivery & Outcomes Research
2.   University of Minnesota

Abstract: Objective: To complete a focused evidence review on key psychometric properties of 17 self-report measures of pain severity and pain-related functional impairment suitable for clinical research on chronic musculoskeletal pain. Methods: Seventeen pain measures were identified to undergo systematic review. Search methods included MEDLINE (1/2000-1/2017), hand-searching (without publication date limits) the reference lists of all included studies, prior systematic reviews, and–when available–Web sites dedicated to each measure (PROSPERO registration CRD42017056610). Our primary outcome was the measure's minimally important difference (MID). Secondary outcomes included responsiveness, validity and test-retest reliability. Outcomes were synthesized through evidence mapping and qualitative comparison. Results: Of 1,635 abstracts identified, 331 articles underwent full-text review, and 43 met inclusion criteria. Five measures (Oswestry Disability Index (ODI), Roland-Morris Disability Questionnaire (RMDQ), SF-36 Bodily Pain Scale (SF-36 BPS), Numeric Rating Scale (NRS) and Visual Analog Scale (VAS)) had data reported on MID, responsiveness, validity and test-retest reliability. Seven measures had data reported on 3 of the 4 psychometric outcomes. Eight measures had reported MIDs, though estimation methods differed substantially and often were not clinically anchored. Conclusions: In this focused evidence review of patient-reported pain outcome measures, the most evidence on key psychometric properties in chronic musculoskeletal pain populations was found for the ODI, RMDQ, SF-36 BPS, NRS and VAS. There was no obvious superiority among measures with respect to psychometric properties in chronic musculoskeletal pain. Choice of measures must depend on study context and goals. Key challenges in the field include substantial variation in methods of estimating psychometric properties, defining chronic musculoskeletal pain, and reporting patient demographics.

Research Topic: Other Chronic Diseases

30. Dissociating the influence of mTBI and PTSD on ventricular volume changes in a military sample

Gullickson, James [1,2]; Kiefer, Jamie [1,2]; Sponheim, Scott [1,2]; Davenport, Nicholas [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Based on the recently proposed relationship between mild traumatic brain injury (mTBI) and chronic neurodegeneration, as well as the high rates of comorbidity between mTBI and post-traumatic stress disorder (PTSD) in military populations, this study tested the hypothesis that mTBI is associated with signs of increased neurodegeneration and that PTSD confounds this association. A sample of 118 Veterans and service members with various combinations of mTBI and PTSD diagnoses was scanned with magnetic resonance imaging (MRI) at two timepoints, and percent ventricular volume change (PVVC) was calculated from T1w MPRAGE images as a proxy for neurodegeneration. Contrary to predictions, those with mTBI experienced slower PVVC rates than those without mTBI, an effect which reached statistical significance only after excluding individuals with PTSD. Also, individuals with accelerated PVVC were identified across the sample, irrespective of mTBI/PTSD grouping. Overall, these results do not support the hypothesis that mTBI is associated with increased neurodegeneration. However, the hypothesis that PTSD confounds the relationship between mTBI and PVVC was partially supported. Directions for future research are proposed to clarify these results.

Research Topic: Dementia & Neuronal Degeneration

31. **Effectiveness of a proactive outreach cessation intervention among socioeconomically disadvantaged smokers: The role of serious mental illness**

Hammett, Patrick [1]; Lando, Harry [2]; Taylor, Brent [1]; Widome, Rachel [2]; Erickson, Darin [2]; Nelson, David [2]; Japuntich, Sandra [3]; Fu, Steven [1]

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3. Brown University

Abstract: Introduction Smokers with serious mental illness (SMI) face barriers to cessation treatment utilization and abstinence at multiple levels of influence. The aim of the present study was to examine whether a proactive outreach intervention that provided facilitated access to cessation treatments was effective for promoting treatment utilization and prolonged abstinence among socioeconomically disadvantaged smokers with SMI. Methods Data were taken from OPTIN, a trial that demonstrated the effectiveness of proactive outreach for promoting treatment utilization and abstinence among smokers enrolled in Minnesota Health Care Programs. The intervention offered telephone outreach, counseling, and free cessation treatments. ICD-9 codes indicating diagnoses of schizophrenic disorders, psychotic disorder, bipolar disorders, and recurrent/severe major depressive disorder were used to categorize participants in SMI (n = 939) or non-SMI (n = 1382) groups. Logistic regressions tested for intervention by SMI interactions on the outcomes. Logistic regressions then modeled the effect of the intervention on treatment utilization and abstinence in both groups Results There were no interactions between the intervention and SMI on any outcomes. Relative to usual care, proactive outreach increased utilization of cessation treatment in the SMI (52.1% vs 40.0%) and the non-SMI group (39.3% vs 25.4%). The intervention also increased abstinence in the SMI (14.9% vs 9.4%) and the non-SMI group (17.7% vs 13.6%). Discussion Proactive outreach is a promising strategy for boosting treatment utilization and abstinence rates among smokers enrolled in publicly subsidized insurance programs. This finding is particularly important for smokers with SMI who tend to utilize more treatments before achieving cessation.

32. **Breathable Prosthetic Socket System**

Hansen, Andrew [1,2]; Koehler-McNicholas, Sara [1]; Barrons, Kyle [1]; Nickel, Eric [1]; Starker, Felix [3]; Mion, Spencer [1]; Ferguson, John [1,2]; Slater, Billie [1]; Voss, Gregory [1]; Ramasamy, Ellankavi [3]

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2. University of Minnesota
3. Fraunhofer Institute

Abstract: Prostheses often use socket and liner materials that have thermal insulating properties (Klute et al., 2007), trapping heat inside the socket and making the residual limb hot, sweaty, and uncomfortable. These hot and moist conditions within the prosthetic socket can exacerbate residual limb skin problems, which reduce mobility and function (Bui et al., 2009). New approaches are needed to make prosthetic socket materials more breathable (Klute et al., 2009), allowing the release of heat and drainage of moisture (Hachisuka et al., 2001). While several powered socket cooling systems are in development (Webber and Davis, 2015; Klute et al, 2016; Ghoseiri et al, 2016), this project aimed to develop passive breathable socket systems that allow evaporative cooling on the residual limb of the prosthesis user. Through several design iterations, our group developed a system that consisted of a breathable liner-sock, a perforated inner socket (holes less than 5mm in diameter) allowing air to penetrate through the socket wall, and an outer frame with large fenestrations in the anterior and posterior aspects. A Veteran with transtibial amputation commented that he could 'feel the air' on his leg while walking with shorts and referred to the system as 'air-conditioned'. Passive breathable socket systems are feasible. Pilot testing of the passively ventilated socket system is ongoing at Walter Reed's National Military Medical Center to determine the feasibility of providing improved socket climate without sacrificing functional mobility.

33. Spiritually Integrated Care for PTSD: A Randomized Controlled Trial of 'Building Spiritual Strength'

Harris, J. Irene [1]; Usset, Timothy [2]; Voecks, Corey [3]; Thuras, Paul [1]; Currier, Joseph [4]; Erbes, Christopher [1]

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2. Center for Veterans Research & Education
3. St. Cloud VA Health Care System
4. University of Southern Alabama

Abstract: Previous literature documents important cross-sectional and longitudinal relationships between spiritual distress and posttraumatic stress disorder (PTSD) outcomes. This study tests the efficacy of a spiritually integrated intervention (Building Spiritual Strength, BSS) that can be delivered by trained chaplains. The intervention addresses spiritual concerns expressed by trauma survivors, including concerns in relationship with a Higher Power, difficulty with forgiveness, and theodicy. In a randomized controlled trial with blinded assessment, participants were randomized to engage in a Building Spiritual Strength condition (n = 71) or Present Centered Group Therapy(PCGT) (control) condition (n = 67) with assessments at baseline, posttreatment, and a two-month follow up. Both groups showed similar, statistically significant reductions in symptoms of PTSD as measured by the Clinician Administered PTSD Scale (CAPS). BSS was shown to be more effective than PCGT in treating distress in relationship with a Higher Power. This was the second clinical trial of BSS with promising results and highlights the need for further study in psychospiritual interventions. More research is warranted on BSS being offered by non-specialized chaplains and on the application of BSS in suicide prevention.

34. Stem cell cardiac patch as an adjunctive therapy during revascularization of Chronically Ischemic Myocardium

Hocum Stone, Laura [1]; Wright, Christin [1]; Swingen, Cory [1]; Chappuis, Erin [1]; Ward, Herbert [1]; McFalls, Edward [1,2]; Kelly, Rosemary [1]

1. University of Minnesota
2. Minneapolis VA Health Care System

Abstract: INTRODUCTION: Clinical studies have shown that functional recovery of Chronically Ischemic Myocardium remains incomplete following surgical revascularization. Mesenchymal stem cells have been shown to improve cardiac function in the peri-infarct region of myocardial ischemia. Our current study tests the therapeutic efficacy of a vicryl-based stem cell patch applied to viable but ischemic myocardium at the time of surgical revascularization. METHODS: Young anesthetized swine underwent thoracotomy with placement of a constrictor around the LAD artery. At 12 weeks, off-pump revascularization was performed with a left internal mammary artery graft to the LAD artery. Animals received adjunctive treatment of either a vicryl patch seeded with MSCs (n = 4), or a vicryl patch alone (n = 4) sutured to the epicardium. 4 weeks later, MRI imaging was performed to assess cardiac function, coronary anatomy, and viability, followed by termination of the animal. MRI studies were performed at baseline and during an infusion of low dose dobutamine (5 µg/kg/min). Low dose dobutamine is used to determine functional reserve. RESULTS: Swine that received the stem cell patch at the time of revascularization showed improvement in regional wall thickening in response to inotropic stimulation, indicating improved recovery of function as compared to revascularization alone. Additionally, the stem cell patch animals showed an increase in regional wall thickening measurements under stress (63.18 ± 21.5 vs 46.67 ± 1.87). Western Blots of the mitochondrial fraction from cardiac tissue showed a significant increase ($p = 0.025$) in expression of ATP synthase (4.18 ± 0.26) as compared to animals who were only revascularized (1.65 ± 0.42). CONCLUSIONS: In a novel large animal model of chronic ischemia, we show for the first time that the combination of an epicardial MSC patch and surgical revascularization results in increased functional recovery of chronically ischemic myocardium compared to revascularization alone. This restoration of function is evident at baseline and under increased workload created by inotropic stimulation. Mitochondrial studies demonstrate an increase in expression of ATP synthase, which may indicate the mechanism of action by which MSCs improve myocardial function.

35. The Relationship Between Auditory Processing and Symptom Dimensions in Patients with Psychotic Disorder

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1. Minneapolis VA Health Care System
2. University of Minnesota, Department of Psychology
3. University of Minnesota, Department of Psychiatry

Abstract: Research on event-related potentials (ERPs) has reliably distinguished auditory processing abnormalities in patients with schizophrenia and bipolar disorder. However, questions remain as to whether these abnormalities can be attributed to specific clinical features, such as psychosis, that may be shared between these disorders. This analysis expands on our previous work on differences in N100 and P300 ERP components, generated by a dichotic listening task, for schizophrenia patients (n = 60), their first-degree relatives (n = 48), and bipolar patients (n = 43), as compared to healthy controls. The patient and relative groups displayed significantly smaller N100 peak amplitudes for all tones compared to controls. Schizophrenia patients displayed significantly larger N100s for rare tones compared to frequent tones. Likewise, the patient and relative groups displayed significantly smaller P300 mean amplitudes for rare tones compared to controls. Additional analyses will expand on these findings by using multiple regression to assess whether group differences in ERP characteristics are attributable to lifetime and current symptom dimensions derived from the Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT), the Brief Psychiatric Rating Scale (BPRS), as well as measures of personality deviation. This analysis will help explore mechanisms by which physiological correlates of auditory processing may contribute to clinical presentation of serious mental illness.

36. Anti-oxidant Therapy and Postoperative Cardiac Events: ACE Trial

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1. Minneapolis VA Health Care System

Abstract: The purpose of the study is to determine whether receiving the antioxidant coenzyme Q10 prior to vascular surgery reduces inflammation levels (measured with biomarkers or blood samples) and troponins (a heart biomarker that indicates heart tissue damage). Patients undergoing vascular surgery have an increased risk of developing cardiac events during or following their surgery. Recent studies have shown that these may be due to an inflammation process that happens following surgery. Additionally, several studies have shown that certain medications may interrupt the inflammation process, thereby decreasing the number of cardiac events. One medication may be an antioxidant called Coenzyme Q10. The hypothesis for this study is 'a brief pretreatment of coenzyme Q10 before elective vascular surgery reduces peak cardiac biomarker elevations, as estimated by a troponin I level at 24 hours post-vascular surgery'. The study will utilize 147 eligible vascular surgical patients in a double blinded placebo vs. Coenzyme Q10 400 mg for 3 consecutive days prior to surgery as a 1:1 ratio. Pre- and post-operative cardiac biomarkers will be collected and subjects followed for 30 days post-operatively for event reporting. Characteristics (n = 127) of participants with an average age of 70 years, mostly Caucasian (92%) males (98%) revealed a high incidence of smoking (43%), coronary artery disease (42%) and diabetes mellitus (38%). Surgical interventions included carotid endarterectomy (24%), EVAR (22%), lower extremity bypass (16%), lower extremity endarterectomy (14%), AAA open repair (10%) and approximately fourteen percent withdrawn due to change in eligibility status or change in course of treatment. Completed enrollment and follow up in March 2018. Data currently in review and analysis.

37. Investigating the effects of DREADD agonists on spontaneous physical activity

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2. Minneapolis VA Health Care System

Abstract: Background: Obesity is a leading cause of preventable death in the United States. In order to develop novel weight loss management strategies, it is imperative to understand brain mechanisms underlying weight loss and physical activity. The orexin neurons within the caudal lateral hypothalamus promote spontaneous physical activity (SPA). Individuals with higher SPA are leaner, and animal studies show that increased SPA prevents weight gain. We used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to activate orexin neurons to increase SPA and reduce body weight. We have previously used clozapine-n-oxide (CNO), thought to be a physiologically inert compound, to activate the DREADDs. However, recent publications suggest that clozapine, a metabolite of CNO, may have independent effects on physical activity. Hypothesis: We hypothesized that higher doses of clozapine would reduce SPA due to off-target effects, but lower doses would activate the DREADDs, without reducing SPA. Methods: Four male and four female orexin-Cre+/- mice (6 months old) were injected with a Cre-dependent AAV vector, containing the DREADD construct. Following acclimation, animals were injected with CNO (1-5 mg/kg) or clozapine (0.001-5 mg/kg) every 48 h, 6 h into the light cycle. Data were analyzed 6, 10, and 24 hour post injection. Results: Clozapine-n-oxide significantly and robustly induced SPA at the 5 mg/kg dose, 24 h post injection ($F_{(5, 35)} = 213.4$, $p < 0.0001$). Similarly, the highest dose of clozapine (5 mg/kg), increased activity at 6 h, but then reduced physical activity at 10 h post-injection ($F_{(5, 35)} = 93.78$, $p < 0.0001$). In contrast, lower doses (0.001-0.1 mg/kg) of clozapine reduced activity by 10 h post-injection. Conclusion: While CNO and clozapine increase physical activity at comparable doses, clozapine reduced physical activity 10 h post-injection, resulting in a failure to increase cumulative SPA over a 24 h period. This suggests that CNO reliably increases daily SPA, making it a better DREADD agonist for the purpose of increasing SPA and reducing weight gain.

38. Longitudinal Reliability of Retrospectively Self-Reported Depression and PTSD Symptoms Among Recent Veterans

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Abstract: Clinical assessment of Posttraumatic Stress Disorder and Major Depressive Disorder is highly reliant on retrospective self-report to appropriately characterize symptom history and course. However, little is known about the reliability of symptom report after several years, especially in the absence of clinical landmarks such as initiation of treatment. In this longitudinal study of recent Veterans (n = 70), the PTSD Checklist-Military Version (PCL-M) and Beck Depression Inventory (BDI-II) were administered at two time points: Baseline symptoms were assessed at an initial research visit 0-3 years after returning from a combat deployment, and a retrospective assessment of the same time period was collected at a second research visit 3-5 years later. Reliability of baseline scores was characterized via hierarchical linear regression of retrospective scores versus other follow-up measures. For both the PCL-M and BDI-II, the current scores at follow-up significantly contributed to the prediction of baseline scores beyond the retrospective reports, suggesting a general underestimation of change over time. Although longitudinal reliability of self-reported symptoms is known to be less-than-perfect, this approach allows more thorough characterization of features that influence retrospective reporting. This direct assessment of a prior time period (at which ground truth is known) could provide direct benefit to clinical assessment.

39. Decreased neural activity in schizophrenia in regions associated with social cognition during an implicit theory of mind task

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2.   Minneapolis VA Health Care System

Abstract: Individuals with schizophrenia (SZ) have deficits in social cognitive processes, including theory of mind (ToM). We investigated the neural correlates of implicit ToM, or the more automatic, less cognitively demanding aspect of this component of social cognition. Fifteen SZ and 21 controls completed an implicit ToM task while undergoing fMRI. Participants watched 20 second videos of two triangles. Movement of the triangles corresponded to three conditions: 1) interacting with each other (i.e., taking each other's thoughts/feelings into account) (ToM); 2) coordinated movement without appearing to take thoughts/feelings into account (physical interaction, PI); and 3) random movement. Participants viewed six videos for each condition across 3 runs, and following each video indicated which type of interaction was going on. Group-level analyses indicated 2 significant clusters of decreased activation in SZ compared with controls for the ToM-PI contrast (corrected cluster significance threshold of $p = 0.05$). Cluster 1 ($k = 3243$) included left postcentral gyrus, temporoparietal junction, and superior temporal gyrus; cluster 2 ($k = 651$) included right superior, middle, and inferior temporal gyri. These regions are broadly consistent with areas involved in social cognition, indicating abnormal neural activity in SZ while engaged in implicit ToM in regions of the brain associated with social cognition.

40. The Role of CK2 in Prostate Cancer

Klein, Mark [1,2]; Blazar, Michael [1,2]; Peltola, Justin [1,2]; Iwamoto, Carlos [1,2]; Gravely, Amy [1]; Kren, Betsy [1,2]; Trembley, Janeen [1,2]; Khalil, Ahmed [1,2]

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Abstract: Introduction. Many patients with stage I or II prostate cancer will progress to metastatic disease despite treatment with curative intent. Current biomarkers to risk-stratify patients for aid in choosing optimal therapy are lacking. Background. The current standard of care for patients with stage I or II prostate cancer, Gleason score of 7 or above, is radical prostatectomy. Despite surgery, many patients will experience progression of the disease, primarily as bone metastases. CK2 is a serine/threonine kinase expressed in all cancers to date. CK2 expression is detectable via immunohistochemistry (IHC) and RNA techniques. Its central role to many oncogenic processes in prostate cancer make it a leading biomarker candidate. Such biomarkers may aid in the determination of who may best benefit from certain adjuvant treatments for resected prostate cancer versus those who may not benefit. Methods and Results. Patients who underwent prostatectomy at the Minneapolis VA Healthcare System (MVA Health Care System) since 1988 were identified. Samples from 9 patients who developed metastases and 12 patients who did not develop metastases were stained with antibodies to CK2-α for IHC. Samples were scored by 2 independent pathologists (blinded) for nuclear stain alone and for combined nuclear/cytoplasmic staining on a scale of 1 (low) to 3 (high). The mean nuclear score for samples from patients with metastatic progression was 1.94 compared with 1.54 for samples from patients with no progression ($p = 0.1044$). However, the mean nuclear plus cytoplasmic score was 2.06 for samples from patients with progression versus 1.54 for samples from patients without progression ($p = 0.0341$). Conclusions. This pilot study demonstrates the feasibility of utilizing IHC to determine whether a correlation between baseline tumor CK2 expression and progression to metastatic disease is present. Early evaluation of a small number of samples suggests a trend that is statistically significant and supports further study of CK2 as a potential biomarker in prostate cancer.

41. Evaluation of a Novel Gait Training Device Using a Pressure Suit to Support Body Weight

Koehler-McNicholas, Sara [1]; Cataldo, Alana [1]; Koch, Elizabeth [1]; Rud, Brittany [1]; Gude, Laura [1]; Brenteson, Charlotte [1]; Johnson, Doug [2]; Wigness, Bruce [2]; Hauck, John [2]; Oddsson, Lars [3]

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2.   Lite Run, Inc.
3.   University of Minnesota

Abstract: Partial body weight-supported (PBWS) gait training is a widely used rehabilitation tool to improve gait function in patients recovering from stroke, traumatic brain injury, or spinal cord injury. In general, the therapeutic quality of PBWS gait training is directly proportional to the amount of time patients can tolerate an upright posture. Factors that limit the therapeutic quality of PBWS gait training include the amount of time needed by physical therapists to set up and deliver therapy with a standard support system (e.g., gait belt, harness lift system) and the fact that standard support systems can be uncomfortable and fatiguing for the patient. To overcome these limitations, Lite Run, Inc. (St. Paul, MN) has developed a novel device for the treatment of patients with gait and balance difficulties. The device consists of two parts: a lower-body suit and a mobile walking frame called the Lite Run Gait Trainer (LRGT). When attached to the LRGT, the lower-body suit uses differential air pressure to effectively unweight the patient up to 50% of their body weight. The goal of this study was to investigate the ability of the LRGT to: 1) provide more efficient rehabilitation (i.e., fewer therapists and less total therapist time while providing at least the same amount of therapy time for the patient) and 2) increase the therapeutic treatment time of patients in an upright position (standing or walking) during a therapy session. Data were collected on nine male Veterans receiving inpatient physical therapy at the Minneapolis VA Health Care System. Subjects completed four consecutive upright gait training sessions according to an ABAB study design (i.e., two sessions each with the LRGT and a standard support system). Overall, subjects demonstrated a two-fold increase in the amount of time they spent upright during a physical therapy session while using the LRGT compared to a standard support system. In addition, the labor efficiency of physical therapists delivering PBWS gait training increased from an average of 21 ± 7% with a standard support system to 56 ± 9% with the LRGT. These results highlight the potential for the LRGT to promote the therapeutic benefits of being upright during physical therapy and demonstrate the capacity for the LRGT to improve the use of hospital resources and reduce labor costs. Future work will focus on outcome measures associated with efficacy and the long-term benefits of using the LRGT in hospital and home care settings.

Research Topic: Central Nervous System Injuries & Associated Disorders

42. Targeting Mitochondrial Thioredoxin 2 for Hepatocellular Carcinoma Therapy

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Abstract: Introduction: New therapy targets for hepatocellular carcinoma (HCC) are critical as liver cancer incidence and death continue to increase and by 2030 HCC will be the 3rd largest cause of cancer death in the US. HCC patients with advanced disease are ineligible for curative ablative therapies and current systemic chemotherapeutics are ineffective in HCC. Background: Increased cellular metabolism and oncogene activation in HCC produces high levels of reactive oxygen species (ROS). As part of clearance of ROS, mitochondrial antioxidant defense (MAD) pathway proteins are significantly upregulated, including thioredoxin 2 (Trx2). Upregulation of the MAD pathway is essential for cancer cell survival as they can't tolerate increased mitochondrial (mt) ROS production as efficiently as normal cell mt. Trx2 also directly regulates other mt functions, preserving mt integrity and preventing apoptosis. Results: The role of Trx2 in HCC cell lines was investigated using gentian violet (GV), a small molecule inhibitor (SMI) of Trx2 and siRNA targeting Trx2 (siTrx2). Treatment of SNU-449, Huh7 and Hep3B HCC cell lines with 250 nM GV for 72h resulted in > than 50% cell death while AML12 nonmalignant hepatocytes retained = 90% viability. Using siTrx2 versus a control siRNA caused 53% ± 1.4% cell death in HepG2 HCC cells. GV induced a large increase in mt ROS in the HCC cells, but not in the nonmalignant AML12 or rat primary hepatocytes. Treatment of HCC cell lines with GV or downregulation of Trx2 using siTrx2 induced loss of Trx2 and reduced FoxM1, cyclin D1 and CDK4 levels in HCC cell lines, suggesting the loss of Trx2 might result in cell cycle inhibition. HCC cell cycle distribution determined by flow cytometry after treatment with GV or siTrx2 showed accumulation of cells in G1 or G2/M phases. The G1 arrest observed with the loss of cyclin D1 and CDK4 occurred in Rb+ Huh7 cells. The Rb mutant Hep3B cells were arrested in G2/M phase consistent with the downregulation of the FoxM1 target genes cyclin B1 and CDK1 preventing completion of G2/M. Conclusions: This data supports the hypothesis that Trx2 is an effective target in HCC, with its loss inducing cell death and arresting cell cycle progression. The data indicates that a substantial pharmacologic window exists for inducing cell death and cell cycle arrest via Trx2 downregulation between HCC cells and nonmalignant hepatocytes, a key consideration in moving a targeted therapy forward to clinical use.

43. The Effect of Intra-Articular Neurotoxin on Arthritis Pain and Substance P Expression in the Dorsal Root Ganglion: Results from Murine Arthritis Models

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1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Background and aims: Substance P (SP) release and binding to NK-1 produces pain transmission. Neurotoxins (NT) that prevent release of SP, such as onabotulinum toxin (BoNT/A), and those that deplete SP, such as vanilloids (VAN), produce analgesia in chronic murine arthritis. This study evaluated the relationship of dorsal root ganglion (DRG) SP expression to pain and analgesia in murine arthritis treated with these NTs. Methods: C57Bl6 male mice received intra-articular (IA) carrageenan, Complete Freund's Adjuvant (CFA) or Collagenase (COL) to produce acute inflammatory, chronic inflammatory or chronic noninflammatory arthritis respectively. IA therapies were given at appropriate intervals before examination. Twelve-week-old mice were examined after arthritis induction. Evoked and spontaneous pain was quantitated. DRGs were harvested for immunohistochemistry (IHC) after pain assessment. SP expression was measured as % DRG neurons expressing SP. Results: Evoked pain in arthritic and naïve mice correlated with SP expression ($R2 = 0.906$, $β = 1.343$). IA vanilloid agonists and antagonist reduced SP expression in a dose dependent manner in chronic inflammatory arthritis (CFA). IA BoNT/A reduced SP expression in CFA arthritis but significantly increased SP expression in COL arthritis at 4 weeks after induction but not at 6 weeks. None of the neurotoxins altered SP expression in non-arthritic mice. Conclusions: Both SP depletion and release inhibition are analgesic in chronic murine arthritis. SP expression varied with NT mechanism of action in COL arthritis at 4 weeks. BoNT/A had different effects on SP expression in 4 week COL and CFA arthritis but SP expression in 6 week COL treated with BoNT/A was similar to that seen in BoNT/A treated CFA. The effect of NT on SP expression may depend on pathophysiology of pain production and chronicity. Understanding the effect of NT treatment on NK-1 expression will be important.

44. Pulmonary Effects of Immediate Versus Deferred Antiretroviral Treatment Initiation in HIV: Final Follow-Up Results from the Randomized Strategic Timing of Antiretroviral Treatment (START) Pulmonary Substudy

Kunisaki, Ken [1]; Niewoehner, Dennis [1]; Collins, Gary [2]; Aagaard, Bitten [3]; Atako, Nafisah [4]; Bakowska, Elzbieta [5]; Clarke, Amanda [6]; Corbelli, Giulio [7]; Ekong, Ernest [8]; Emery, Sean [9]; Finley, Elizabeth [10]; Florence, Eric [11]; Infante, Rosa [12]; Kityo, Cissy [13]; Madero, Juan Sierra [14]; Nixon, Daniel [15]; Tedaldi, Ellen [16]; Vestbo, Jørgen [17]; Wood, Robin [18]; Connett, John [2]

1. Minneapolis VA Health Care System
2. University of Minnesota
3. Copenhagen HIV Programme
4. Medical Research Council
5. Wojewodzki Szpital Zakazny
6. Royal Sussex County Hospital
7. European AIDS Treatment Group
8. Institute of Human Virology-Nigeria
9. Kirby Institute
10. Washington DC VA Medical Center
11. Institute of Tropical Medicine
12. Asociación Civil Impacta Salud y Educación
13. Joint Clinical Research Center
14. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
15. Virginia Commonwealth University
16. Lewis Katz School of Medicine at Temple University
17. University of Manchester
18. Desmond Tutu HIV Foundation

Abstract: Rationale: We have previously shown, using a randomized controlled study design, that among HIV-positive individuals, naïve to antiretroviral treatment (ART) with baseline CD4 counts > 500 cells/mm3 who enrolled in a pulmonary substudy, there was no difference in rate of lung function decline between those randomized to immediate ART initiation versus ART initiation at a CD4 count of 350 cells/mm3. The parent study was unblinded early due to clear benefits to immediate ART in reducing AIDS and non-AIDS events. At unblinding, median follow-up in the pulmonary substudy was only 2.0 years. We continued follow-up through the end of December 2016 and now present final substudy results. Methods: Participants were enrolled from 80 sites in 20 countries. Participants were > 25 years old, naïve to ART, with CD4 counts > 500 cells/mm3, not receiving asthma treatment, and without recent respiratory infections. Participants were randomized to receive ART either immediately or deferred until CD4 counts decreased to 350 cells/mm3. Spirometry was performed prior to randomization and then annually. The primary outcome was rate of lung function decline, expressed as the forced expiratory volume in 1s (FEV1) slope in mL/year. Results: 1,026 participants were randomized to immediate (n = 518) or deferred (n = 508) ART. Median baseline characteristics included age 36 years (IQR 30-44), CD4 count 648 cells/mm3, HIV RNA 4.2 log10 copies/mL, and known duration of HIV infection 1.2 years. 29% were female and 28% were current smokers. Median follow-up time was 3.9 years. We found no difference between the immediate and deferred ART groups in FEV1 slope among smokers (difference of +2.8 mL/year; 95%CI: -21.1 to +26.7) or non-smokers (difference of -5.2 mL/year; 95%CI: -17.1 to +6.7). Results were nearly identical when excluding spirometry tests that did not meet quality standards (4.6% of tests). There was no difference in total St. George's Respiratory Questionnaire (SGRQ) scores between immediate and deferred ART. The SGRQ symptom domain favored immediate ART in smokers (difference of 3.5 points [95%CI: -6.5 to -0.5]), but not in non-smokers; others domains showed no difference in smokers or non-smokers. Conclusions: Among this relatively young sample of HIV-positive persons, naïve to ART, with CD4 counts > 500 cells/mm3, timing of ART initiation had no major effect on lung function decline or respiratory health status.

Research Topic: Infectious Diseases
Funding agencies: NIH

45. Post-Traumatic Visualized Supernumerary Phantom Limbs: A Case Report

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1.   University of Minnesota

Abstract: Case Description The patient is a 38 year old male Veteran with a history of traumatic brain injury (TBI) 10 years prior to presentation with resultant post-traumatic epilepsy. Following a medication change, he was in a severe traffic collision attributed to seizure activity. Extensive polytrauma injuries resulted, most notably C4 complete tetraplegia, a new TBI, and cerebellar infarcts. Post-traumatically, the patient reported constantly feeling and visualizing additional arms sprouting from elbow height bilaterally. These extra arms moved independently of his true arms and were visualized even with his true arms covered. Consultants from Psychiatry, Neurology and Ophthalmology could not find any alternate diagnoses for this experience and he was diagnosed with visualized supernumerary phantom limbs (SPLs). Three months post-traumatically, he spontaneously began experiencing supernumerary phantom legs, sprouting medially from his knees bilaterally, after a suspected seizure. EEG at that time recorded left occipital epileptiform activity. Discussion Supernumerary Phantoms limbs are a rare phenomenon known to occur following a variety of neurological ailments including stroke, spinal cord injury, epilepsy, TBI, space occupying lesion, cervical root avulsion and demyelinating disease. Less than thirty cases of SPLs have been reported and of those, only six cases described visualized SPLs, all of which were in the setting of isolated stroke. While it is currently not possible to establish the primary etiology of our patient's visualized SPLs, given that he experienced acute and chronic TBIs, SCI, stroke and acute and chronic seizures, the later development of his new lower extremity SPLs with corresponding left occipital epileptiform activity seems to heavily suggest seizure activity as the primary contributor to his SPL experience. Conclusions This case report describes what appears to be the first reported case of visualized supernumerary phantom limbs in a polytrauma patient.

Research Topic: Acute & Traumatic Injury
Funding agencies: N/A
Grant support: N/A

46. From 'End of Urology' to Endourology: Urologic Legacy of the Minneapolis VA

Lane, Giulia [1,2]; Uloko, Maria [1,2]; Narayan, Vikram [1,2]; Ercole, Cesar [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Introduction: Many leaders in Urology have trained or served at the Section of Urology within the Minneapolis Veterans Affair (VA) and innovations such as the Gleason score, development of testicular tumor markers, the Fuhrman grading system, and Endourology have had their roots at this institution. Herein we recount the Urologic contributions of the Section of Urology at the Minneapolis VA. Methods: A review of Urologic literature from the Minneapolis VA from 1946 to present. Results: The Minneapolis VA Section of Urology has trained residents in Urology since its affiliation with the University of Minnesota in 1946. Notable urologic accomplishments at the Minneapolis VA include the development within the field of Urologic Oncology, pioneering of Endourology, and evidence based urologic guidelines. Since 1946, there have been a dozen Urologists who trained or served at the Minneapolis VA and continued on to be head of Urology Departments.

Research Topic: Health Systems
Funding agencies: N/A
Grant support: N/A

47. Brain glucose metabolism and amyloid deposition in healthy elderly APOE4/E4

Lee, Joel T. [1]; Pardo, Jose V. [1,2]; Alzheimer's Disease Neuroimaging Initiative

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Alzheimer's disease (AD) progresses insidiously over decades before the patient comes to clinical attention. Therefore, study of preclinical AD is critical to identify early pathophysiological changes as potential targets for prevention or treatment. The brain processes at the preclinical stage remain minimally understood. Aside from age, the E4 allele of APOE flags a group at particularly high risk of late-onset AD (LOAD). The E4 allele has the highest effect size for disease risk of any known common genetic variant. Studies of these individuals could provide insights about the ontogenesis of AD offering clues for novel treatment strategies. To this end, cognitively normal, APOE*E4 homozygotes from the Alzheimer's Diseases Neuroimaging Research Initiative database (ADNI-LONI) provided fluorodeoxyglucose and amyloid (florbetapir) PET scans (n = 8 and 7, respectively; mean age 76 years). Their scans were compared to those of age-matched, cognitively normal elders who were not E4 carriers. There was dissociation in the distribution between glucose uptake and amyloid deposition in the homozygotes. In other words, areas with dense amyloid deposits were not necessarily hypometabolic. Peak hypometabolism localized bilaterally along the medial temporal cortex. In contrast, peak amyloid deposition localized principally to the putamen, a finding also seen in preclinical carriers of autosomal dominant, early onset, AD mutations as well as preclinical AD associated with Down's syndrome. Additional regions of amyloid deposition in homozygotes were medial prefrontal cortices including the anterior cingulate cortex, middle and inferior frontal cortices, and middle and inferior occipital cortices. These findings contrast with those reported for LOAD (typically age > 65 years) where hypometabolism and amyloid deposition localize principally to the posterior cingulate cortex. These data begin to characterize elders with normal cognition despite high AD risk in comparison to the known phenotypes of patients with LOAD. The alterations seen here in cognitively intact elders differ from those seen in LOAD and may reflect selection bias, small sample size, or altered pathophysiology in the homozygotes.

48. VA Traumatic Brain Injury Model Systems: 2018 Local Update

Leese, Mira [1]; Simonson, Adam [1]; Finn, Jacob [1]; Lamberty, Gregory [1]

1.   Minneapolis VA Health Care System

Abstract: The Traumatic Brain Injury Model System (TBIMS) project is a prospective, 20-year longitudinal, multi-center study which examines TBI recovery and outcomes following coordinated acute medical care and inpatient rehabilitation. In 2008, the Department of Veterans Affairs Polytrauma Rehabilitation Centers (VAPRCs) joined TBIMS and has enrolled over 1,100 Veterans nationwide. The Minneapolis PRC site has enrolled 145 Veterans, and the initial participants are passing their Year 5 follow-ups. Individuals (18 years old or older) who are admitted to the Minneapolis VA PRC or Polytrauma Transitional Rehabilitation Program (PTRP) for inpatient rehabilitation following a mild, moderate, or severe TBI are eligible for study participation. This study seeks to provide an update on the Minneapolis cohort progress. The information obtained from this study will translate to better understanding long-term implications of TBIs as well as improving programs within the VA PRC health care system. Upcoming projects, future directions, dissemination and modules will be discussed.

49. **Posttraumatic Stress Disorder is Associated with Explicit Rather Than Implicit Verbal Memory Performance Deficits in U.S. Military Veterans**

Marquardt, Craig [1]; Pokorny, Victor [1]; Disner, Seth [1]; Nelson, Nathaniel [2]; Sponheim, Scott [1]

1.   Minneapolis VA Health Care System
2.   University of St. Thomas

Abstract: Veterans with posttraumatic stress disorder (PTSD) often report disrupted cognition. Verbal learning and memory are well-established domains of impairment in PTSD. The underlying mechanisms behind PTSD-related verbal memory deficits are poorly understood as are the potential influences of common comorbid conditions such as mild traumatic brain injury (mTBI). We report results from two cross-sectional studies of OEF/OIF Veterans recruited from the Minneapolis VA Health Care System using both laboratory and conventional neuropsychological assessments of verbal memory. As expected, Veterans with PTSD exhibited reduced performance on explicit/declarative verbal memory tasks, but no differences were observed in implicit/procedural memory-based repetition priming. We observed independent effects of hippocampal tail volume size on explicit verbal memory performance, but these associations did not mediate the effects of PTSD. No effects of blast-related mTBI were observed. The results highlight the importance of considering the influence of PTSD-related processes among Veterans when assessing memory functioning post-deployment.

50. **Assessment of Antimicrobial Susceptibility Testing Profiles of Urine Isolates from Veterans to Guide Empiric Therapy for Suspected Urinary Tract Infection**

Marsh, Ketzela [1]; Mundy, Lesley [2]; Holter, John [2]; Johnson, James [1,2]

1.   University of Minnesota
2.   Minneapolis VA Health Care System

Abstract: Background: Urinary tract infection (UTI) is common among patients at Veterans Affairs Medical Centers (VA Medical Centers), many of whom are elderly men with underlying medical or urological problems. Most UTI treatment guidelines address uncomplicated UTI in women and presume knowledge of local antimicrobial susceptibility testing (AST) patterns for uropathogens, which often are unknown or are inferred from E. coli. To inform selection of empiric therapy for UTI at our VA Medical Center, we compiled AST data for one year's urine isolates. Methods: We compiled AST results (bioMerieux VITEK®) for the 2,494 significant urine isolates from the Minneapolis VA Medical Center clinical microbiology laboratory from June 2013 through May 2014. For 'drug-bug' combinations that were not tested we imputed results based on local or published data, and/or expert opinion. We then calculated cumulative % susceptible for 25 relevant antimicrobial agents, overall and stratified by Gram stain group and clinical site (intensive care unit, inpatient, outpatient, community residential centers, or extended care). In ambiguous situations susceptibility was analyzed as both 0% and 100%. Results: The 2,494 urine isolates included 946 Gram-positive and 1,548 Gram-negative organisms. Species distribution varied significantly by clinical site. E. coli represented only 27% of isolates overall (9-37%, depending on site). Enterococcus (14%) and other Gram-positives (23%) were also prevalent. Cumulative AST profiles varied significantly (i) by Gram stain group, (ii) between E. coli and other Gram-negatives, and (iii) by clinical site. No tested oral agent provided = 80% overall susceptibility. Although AST data were unavailable for fosfomycin, imputation suggested 82%-95% susceptibility overall. Conclusion: Among urine isolates from Veterans, E. coli was a minor contributor and a poor surrogate for total population AST profiles. The only oral agent that provided = 80% susceptibility overall was fosfomycin, suggesting that it could be an important option for empiric lower UTI therapy for Veterans. Urine isolate-specific antibiograms that reflect local AST data, stratified by Gram stain group and clinical site, could improve empirical UTI therapy for Veterans, as could performance of urine Gram stains.

51. Assessment of Sub-Concussive Load in Minnesota Army National Guard Soldiers

Martin, Kathleen [1,2]; Kiefer, Jamie [1,2]; Davenport, Nicholas [1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: Past research of head injury in military populations has focused heavily on mild traumatic brain injuries and may not account for sub-concussive injuries. While the effects of a traumatic brain injury might be more immediately evident, an accumulation of cranial impacts that may not result in concussion might also lead to lasting effects. Initial findings have been mixed, but there is some evidence of an association between sub-concussive load and diminished processing speed, reduced working memory, and slower reaction times. This makes it imperative that research be conducted on how an individual's history of sub-concussive impacts, such as those obtained during sporting events, may affect their experience and performance in the military. The present study aims to assess the association between sub-concussive load as it relates to training outcomes in a sample of Minnesota Army National Guard Soldiers (n = 185). Soldiers are assessed for history of sub-concussive load and athletic history before and after completion of basic combat training using the Assessment of Sub-Concussive Load (ACSL). Initial findings have yielded few significant findings, however future iterations of the ACSL will aim to increase the quantitative nature of retrospective reporting on sub-concussive head impacts.

52. The Impact of PTSD and mTBI on the Relationship Between Subjective and Objective Deficits in Combat-Exposed Veterans

Mattson, Elsa [1]; Disner, Seth [1]; Nelson, Nathaniel [2]; Sponheim, Scott [1]

1. Minneapolis VA Health Care System
2. University of St. Thomas

Abstract: Veterans with post-traumatic stress disorder (PTSD) and/or mild traumatic brain injury (mTBI) frequently endorse subjective cognitive complaints. However, the relationship between subjective complaints and objective cognitive performance has been variably characterized in the literature to date. This study aimed to clarify the extent to which PTSD and mTBI impact the relationship between subjective and objective cognition. In a sample of 231 combat-exposed Veterans, we assessed PTSD symptom severity, history of blast and impact mTBI, objective neuropsychological test performance, and subjective cognitive complaints. Initial results indicated that more subjective cognitive complaints predicted worse performance on neuropsychological tests. When controlling for PTSD, blast mTBI severity, and impact mTBI severity, the association between subjective complaints and objective performance became non-significant. PTSD was positively associated with subjective complaints, while blast mTBI was negatively associated with cognitive complaints, which was not in the expected direction. Subjective complaints were unrelated to impact mTBI. Our results suggest that PTSD symptom severity is strongly related to subjective complaints regardless of actual cognitive functioning, but the relationship between blast mTBI and subjective cognition is more complex and deserving of further research.

53. Drug-Eluting Stents vs. Bare Metal Stents in Saphenous Vein Graft Angioplasty (DIVA)

McFalls, Edward [1]; Garcia, Santiago [1]; Johnson, Debra [1]; Condon, Debra [1]; Brilakis, Emmanouil [2]; Banerjee, Subhash [2]; Ventura, Beverly [3]; Rangan, Bavana [2]

1. Minneapolis VA Health Care System
2. VA North Texas Health Care System
3. VA Palo Alto Health Care System

Abstract: VA Cooperative Studies Program #571 was designed to prospectively evaluate the efficacy of drug-eluting stents (DES) in reducing aortocoronary saphenous vein bypass graft (SVG) failure when compared to bare metal stents (BMS) in patients undergoing stenting of de novo SVG lesions. SVGs often develop luminal stenoses that are most commonly treated with stent implantation. Approximately 60,000-100,000 percutaneous SVG interventions are performed annually in the USA. Two types of coronary stents are currently available: bare metal stents and drug eluting stents. Bare metal stents are the standard of care for the percutaneous treatment of SVG lesions, but are limited by high rates of in-stent restenosis (as high as 51% after 12 months) often leading to repeat percutaneous or surgical SVG treatments. Drug-eluting stents have been shown to significantly reduce in-stent restenosis and the need for repeat target vessel and lesion revascularization in native coronary arteries, yet their efficacy in SVGs is not well studied, with conflicting results from various small studies. The Cooperative Studies Program study will be the first large prospective, randomized, multicenter, blinded clinical trial without routine angiographic follow-up comparing DES and BMS in SVG lesions. Study Aim of Hypotheses: DES will reduce the 12-month incidence of target vessel failure (TVF, primary study endpoint) compared to BMS. TVF will be defined as the composite of cardiac death, target vessel myocardial infarction and target vessel revascularization, and is the primary clinical endpoint used in all FDA-approved DES pivotal trials. Design & Methods: At the 26 participating VA hospitals, patients with prior coronary artery bypass graft surgery scheduled to undergo coronary angiography and/or percutaneous intervention to a SVG were screened. Patients who needed SVG stenting and who meet all the inclusion and none of the exclusion criteria were asked to participate in the study. They were randomized to one of two types of stents. Cardiac biomarkers were collected prior to and post stent placement. 12 Months of ADP P2Y12 Inhibitor Treatment. Follow up visits were completed every 6 months through study completion. Conclusions: When stenting de novo SVG lesions, no significant difference in long- and short-term outcomes between DES and BMS. Novel strategies are needed for treatment of severe SVG lesions.

54. The Association of Communication Characteristics and Risk Perception with Smoking Behaviors among Patients with Incidentally Detected Pulmonary Nodules

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1. Minneapolis VA Health Care System
2. Edith Nourse Rogers Memorial Veterans Hospital
3. Boston University School of Medicine
4. Portland VA Medical Center

Abstract: Rationale: Studies suggest that identification of a nodule during lung cancer screening is associated with smoking cessation through an unclear mechanism. This association is not well established for incidental pulmonary nodules (IPNs). We report planned analyses of characteristics associated with smoking behaviors among this group. Methods: Prospective, repeated-measure, cohort study of smokers and recent quitters with new IPNs treated within the VA Portland Health Care System from 2011-2015. At baseline, patients reported heaviness of smoking, stage of change (SOC), and metrics of anxiety and communication with the clinician who provided care for the IDPN, usually a primary care provider. Smoking and SOC measures were repeated throughout the period of nodule follow-up (per usual clinical care, up to two years after detection). Change in smoking behavior was 'positive' if patient stayed quit, cut down, or made a quit attempt, otherwise 'negative'. SOC was categorized as 'positive' if patients were thinking of or planning to quit, making an attempt, or had quit, otherwise 'negative'. We used generalized estimating equations clustered on participant to estimate longitudinal associations between smoking behavior and SOC, and communication quality, distress regarding the nodule, perceived risk of lung cancer, and cessation interventions. Analyses adjusted for age, income, and depression. Results: Of 121 patients with IPNs, 46 were current smokers, with 9 past-year quitters. 43 patients (36 smokers, 7 recent quitters) were analyzed, comprising 127 follow-up assessments. By the final visit, 8/36 (22%) of the smokers had quit and 2/7 (29%) of quitters relapsed. 58% (23/40) of respondents received quit support from a provider at least once. Most participants reported at least one positive change in smoking (31/43, 72%) or SOC (37/43, 86%). Positive SOC was associated with positive change in smoking behavior (OR 6.1, p = 0.008). In adjusted analyses, we found no significant associations of communication quality, distress, perceived lung cancer risk or smoking cessation treatments with smoking behaviors or SOC. (Table) Conclusions: Smokers with tracked IPNs quit and relapsed frequently during nodule follow-up, though many received no quit support. We found no associations between program-modifiable characteristics and quit behavior. Tobacco-specific messaging – as recommended for all patient encounters – may benefit patients with IPNs.

55. Prospective Predictors of Chronic Pain among U.S. National Guard Soldiers

Miron, Lynsey [1,2]; Hagel-Campbell, Emily [2]; Noorbaloochi, Siamak [2]; Donaldson, Melvin [1,2]; Krebs, Erin [1,2]; Erbes, Christopher [1,2]; Arbisi, Paul [1,2]; Polusny, Melissa [1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota Medical School

Abstract: Despite the high prevalence of chronic pain among Veterans receiving VA health care, the development of chronic pain remains poorly understood. A better understanding of factors affecting pain outcomes is needed to inform prevention and intervention strategies. A prospective cohort of OEF/OIF deployed U.S. National Guard soldiers (n = 1,351) completed three survey waves (pre-deployment, 3 months post-deployment, 3-8 years post-deployment) assessing predisposing risk factors for pain development and adjustment. At follow-up, Veterans were categorized by the Graded Chronic Pain Scale: no pain (n = 942; 70%), low disability pain (n = 149; 11%) and high disability pain (n = 260; 19%). ANOVA planned comparisons revealed significant effects of several pre-deployment vulnerability factors, deployment-related stressors, and post-deployment mental health symptoms on pain outcomes, where the most robust differences emerged between the no pain and high disability pain groups. Logistic regression and relative weights analysis showed pre-deployment somatization and neuroticism, perceived difficult deployment environment, and post-deployment mental health were the strongest predictors of chronic pain development. Among soldiers with chronic pain, post-deployment coping behavior and PTSD symptoms were the strongest predictors of chronic pain disability, where acceptance-based coping (i.e., activity engagement and pain willingness) was associated with low disability pain. Findings suggest that while pre-disposing risk factors may influence the development of chronic pain, targeting pain-related acceptance may support adaptive adjustment.

56. Million Veteran Program (MVP): A Partnership with Veterans

Murdoch, Maureen [1]; Vang, Derek [1]; Eret, Donyal [1]; Condon, Debra [1]; Kantorowicz, Alexandra [1]

1.   Minneapolis VA Health Care System

Abstract: Purpose: The goal is to improve Veterans' health through the collection and testing of blood samples and health information to learn which genes are linked to which health characteristics. MVP is a national, voluntary research program conducted by the Department of Veterans Affairs, Office of Research & Development, that collects genetic and health information to help find new ways of prevention, early detection, and treatment of illnesses. MVP will provide a better understanding of how genes affect health and illness, with the goal of improving health care for Veterans. Genomic analyses, including SNP genotyping, whole genome sequencing, and whole exome sequencing is being conducted on MVP samples. Nationally, 661,076 Veterans have enrolled at 55 VAs with 15,646 at the MVA Health Care System as of 4/16/18. Methods: Participation involves: 1. Filling out two surveys through the mail 2. Completing a one-time, approximately 20 minute, study visit to provide a blood sample for the genetic testing 3. Permitting authorized MVP staff to access information in your medical record on an ongoing basis 4. Agreeing to future MVP contact Next Steps - MVP Data Analysis: The first projects approved to utilize the MVP data are focused on issues that are relevant in our Veteran community. These studies will not only provide valuable research results, but are also helping to develop and streamline the data access procedures for future researchers. Current Studies (*Coordinated by VA Boston & VA CT Health Care Systems): • The Genetics of Functional Disability in Schizophrenia and Bipolar Illness*, Bronx VA Medical Center; Miami VA Medical Center • Genomic Study of Posttraumatic Stress Disorder*, San Diego VA Medical Center; VA Connecticut Health Care System • Genomics of Gulf War Illness in Veterans*, VA NJ Health Care System; VA Cooperative Studies Epidemiology Center Durham • Genetic Vulnerability of Sustained Multi-substance Use in MVP, VA Connecticut Health Care System; Philadelphia VA Medical Center • Cardiovascular Disease Risk Factors, Prevalent Cardiovascular Disease, and Genetics in the Million Veteran Program, Atlanta VA Medical Center; Boston VA Health Care System • Pharmacogenomics of Risk Factors and Therapies Outcomes for Kidney Disease, VA Tennessee Health Care System • Genetics of Cardio-metabolic Disease in the VA Population, VA Palo Alto Health Care System; Philadelphia VA Medical Center • Genetic Risk for AMD in Diverse Veteran Populations, Cleveland VA Medical Center; VA Western NY Healthcare System

Research Topic: Personalized Medicine & Genomics

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57. Impact Testing of High-Activity Prosthetic Feet

Nickel, Eric [1]; Morin, Steve [1]; Koehler-McNicholas, Sara [1]; Hendershot, Brad [2]; Schnall, Barri [3]; Hansen, Andrew [1,4]

1.   Minneapolis VA Health Care System
2.   Walter Reed National Military Medical Center
3.   DOD-VA Extremity Trauma and Amputation CoE
4.   University of Minnesota

Abstract: Not all prostheses are created equal. With the rise in numbers of Veterans with lower limb amputation seeking to return to active duty military service, it is critical to understand the behavior of prosthetic feet and other components under anticipated military use conditions. These conditions are also present in many high-impact civilian professions such as farming or construction. At present, there is no impact testing standard for prostheses, yet navigating obstacles or rapidly exiting a vehicle would lead to significant impact loading on the prosthesis. To assess the performance of prosthetic feet under these conditions, we designed and built a test system capable of achieving impact heights that surpass the ground clearance of the tailgate of a High-Mobility Multi-Wheeled Vehicle (HMMWV, 0.84-0.88 meters) which is a common height that soldiers would jump from. Three samples each of nine prosthetic feet intended for high activity amputees were dropped from heights ranging from 10cm to over 100cm in increments of 10cm until failure was detected. The maximum drop height that each sample withstood is reported along with average values for each product. The drop heights that each sample withstood ranged from 20cm to 100cm (failed at 30cm and 110cm respectively). The averages ranged from 27cm to 73cm. Three of the feet consistently outperformed the other six, suggesting that certain designs are more robust to impact loading than others and may be more appropriate for Veterans engaging in high impact activities, such as farming or returning to military service.

Research Topic: Acute & Traumatic Injury

58. Acceptability and Feasibility of Repeated Transcranial Direct Current Stimulation (tDCS) as an Intervention for Individuals with Mild Traumatic Brain Injury

Nienow, Tasha [1]; Yamada, Torricia [1]; Gilmore, Casey [1]; Lamberty, Gregory [1]; Nelson, Nathaniel [2]; MacDonald, Angus [3]; Thuras, Paul [1]; Lim, Kelvin [1,3]

1. Minneapolis VA Health Care System
2. University of St. Thomas
3. University of Minnesota

Abstract: Purpose: Transcranial direct current stimulation (tDCS) is a non-invasive technique that has become the focus of intense study in recent years due to its potential as a cognitively enhancing intervention. Presently, very little is known about patient perception of this intervention approach. This project assessed the acceptability and feasibility of offering repeated tDCS as an intervention for cognitive difficulties to individuals with mild traumatic brain injury (mTBI). Methods: Recruitment of individuals with mTBI for a 24-session study of tDCS concurrent with cognitive training began in November 2016. Information about the study was sent to 833 individuals. Response to the advertisement, patient eligibility, and rate of treatment uptake were reviewed to assess intervention acceptability and feasibility. Results: Potential participants were receptive to tDCS as an intervention approach and were rarely excluded due to criteria specific to the tDCS intervention. However, among individuals with mTBI, interest in an intensive intervention was modest and many identified environmental barriers to participating in multiple sessions a week. Conclusions: Results provide insights into patient motivation for an intensive, cognition-focused intervention among individuals with mild traumatic brain injury as well as a better understanding of potential treatment barriers.

59. Utility of Nuclear Stress Imaging in predicting long-term outcomes one-year post CABG Surgery.

Ortiz, Fernando [1]; Mbai, Mackenzi [2]; Adabag, Selcuk [2]; Garcia, Santiago [2]; Nguyen, Jennifer [2]; Goldman, Steven [3]; Ward, Herbert [2]; Kelly, Rosemary [2]; McFalls, Edward [1,2]

1. University of Minnesota
2. Minneapolis VA Health Care System
3. Southern Arizona VA Health Care System

Abstract: Background: Quantification of defect size with stress imaging may have promise in risk-stratification among asymptomatic patients following CABG. Methods: At a single center participating in a VA Cooperative Study Program (CSP #474) on graft patency, patients underwent stress imaging at 1-year following CABG. Stress tests were performed on the same day as the angiogram and reviewers were blinded to patient study arm. Semi-quantification of defect size was categorized as none, mild, moderate and severe. Results of the angiogram were categorized as either the presence or absence of a significant graft stenosis. Long-term end-points include the composite of death and congestive heart failure. Results: Eighty-four participants underwent SPECT and angiography. Graft disease was identified in 39 patients involving 56 of 251 graft sites (22%) and compared to those individuals with no graft disease, did not predict long-term adverse outcomes (p = 0.29). Three separate stress SPECT-MPI findings predicted adverse outcomes: inability to reach stage 3 of a Bruce protocol (OR 7.3 CI 2.4-22.1, p < 0.001), LVEF < 45% (OR 4.0 CI 1.1-15.3, p = 0.041) and a moderate large stress defect size(HR 2.31 CI 1.1-1.5 p = 0.04) for the composite end-point. These findings appear to be additive and strongest among patients who underwent exercise stress testing with Cox hazard models yielding a hazard ratio of 10.6 (p < 0.001). Conclusion: Stress imaging with SPECT-MPI, in clinically stable patients who have undergone prior CABG, may have utility in risk-stratification. Among these higher risk individuals, consideration of interventions that can modify either sudden death or heart failure may be important.

60. Cognitive Aging and the role of the Anterior Cingulate Cortex

Pardo, Jose [1]; Lee, Joel [1]; Vorobyov, Yelena [1]; Nyabwari, Shantal [1]; Hill, Meghan [2]; Eliason, Jackson [3]; Honsey, Blair [4]

1.   Minneapolis VA Health Care System
2.   University of Minnesota
3.   University of St. Thomas
4.   University of Saint Mary

Abstract: The goal of this research program is to understand the biology of cognitive aging so as to prevent or treat it. The fundamental hypothesis for this project posits the anterior cingulate cortex (ACC) plays an early and pivotal role in cognitive aging through dysfunction of its metabolism and/or of its functional connectivity to related neural networks. Corollary hypotheses include the following: 1) Elders will show evidence of resting ACC hypometabolism even at the level of the individual, providing a potential biomarker for age-associated cognitive decline (AACD). 2) ACC metabolism will decline with aging and APOE4 genotype and will further anticipate conversion to mild cognitive impairment (MCI), a condition that precedes Alzheimer's disease. 3) ACC metabolism will correlate best with tests of executive rather than mnemonic functions. To accomplish these goals, the project has the following specific aims: 1) Characterize in a cross-sectional design resting ACC hypometabolism and functional connectivity in matched groups of carefully characterized healthy young and related elder subjects (i.e., child/parent pairs). 2) Model in a longitudinal design using existing normative ADNI data resting ACC metabolism as a function of age, APOE genotype, education, etc. and determine whether ACC hypometabolism predicts those who convert to MCI. 3) Characterize the cognitive sequelae of aging-related ACC hypometabolism. Acknowledgements: 1. Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. 2. This work was funded by VA 5I01 CX000501 (JVP). This material is the result of work supported with resources and the use of facilities at the Minneapolis Veterans Health Care System, Minneapolis, MN. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

61. Anterior Cingulate Cortical Metabolism at Rest is a Mediating Factor in the Relationship between Age and Executive Function in Healthy Elderly Independent of Amyloid Deposition

Pardo, Jose V. [1,2]; Lee, Joel T. [1]; Nyabwari, Shantal [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: It is important to identify and understand the role of potential biomarkers for cognitive decline in the elderly. We showed previously the anterior cingulate cortex (ACC) is key to aging-related metabolic dysfunction correlating with AACD (Pardo et al., 2007). Here, we examine using the ADNI dataset the hypothesis that ACC metabolism functions as a mediator in the age and executive function relationship driven by amyloid deposition. This suggests the decline in ACC metabolism with age is an important explanatory factor in the observed age and cognition relationship related to the neural dysfunction induced by fibrillar amyloid during otherwise healthy aging. FDG and PET scans were obtained from ADNI, and were stereotactically normalized to standard Talairach space via the Neurostat program (S. Minoshima, U. Washington). We performed a region-of-interest (ROI) analysis for each scan. We obtained data from 231 cognitively normal participants (age 59-93 years, mean 74, SD 6). Participants' ages and animal fluency scores, which served as a measure of executive performance, were also obtained from ADNI and were matched to their respective ACC amyloid SUVr and FDG uptake ROI means. In agreement with our previous study, there were significant correlations between age and metabolism [$r = -0.44$, $p = 2(10)-12$]; metabolism and fluency [$r = -0.23$, $p = 4(10)-4$]; and age and fluency [$r = -0.26$, $p = 2(10)-4$]. These findings motivated a mediation model in which ACC metabolism functions as a mediator in the age and fluency scores relationship. The Sobel test for mediation showed significance in the indirect effect of ACC metabolism on the age and fluency relationship at the .05 significance level, suggesting ACC metabolism functions as a mediator in the age and fluency relationship. The direct effect or the effect of age on fluency when controlling for ACC metabolism was not zero. As such ACC metabolism is a partial mediator between age and fluency, not a complete mediator. There was no significant correlation between age and amyloid ($r = 0.12$, $p = .06$) or amyloid and fluency ($r = 0.09$, $p = .17$). Surprisingly, resting metabolism was positively correlated with amyloid in these healthy elders ($r = 0.15$, $p = .02$). The results show that ACC metabolism in part is a mediator in the age and cognitive function relationship, and support the creation and use of novel interventions targeting the ACC to prevent or treat the decline in cognitive function associated with normal aging.

62. Physiological responses to aversive combat visual stimuli associated with PTSD

Pokorny, Victor [1]; Marquardt, Craig [1,2]; Kang, Seung Suk [3]; Sponheim, Scott [1,2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota
3.   University of Missouri Kansas City

Abstract: Posttraumatic stress disorder (PTSD) is associated with attentional control abnormalities and emotional dysfunction, especially with respect to trauma-related stimuli. The present study examined neural activity using event-related potentials (ERPs) in a cross-sectional sample of recently deployed U.S Veterans from Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF; n = 71). Veterans were administered the Clinician-Administered PTSD Scale (CAPS) and Minnesota Blast Exposure Screening Tool (MN-BEST) to assess PTSD symptom severity and mTBI blast severity, respectively. CAPS scores were summed to reflect four symptom groupings: Hyperarousal, Intrusions, Dysphoria, and Avoidance. Electroencephalography recordings were obtained during presentations of pleasant, neutral, unpleasant and aversive combat-related images at the posterior Pz and anterior Fpz electrode sites. At Pz sites, higher hyperarousal scores were associated with reduced late positive potential (LPP) amplitudes during combat conditions. At Fpz sites, higher hyperarousal scores were associated with reduced P2 amplitudes during pleasant conditions. Additionally, at Fpz sites, greater intrusion symptoms were associated with reduced P3 mean amplitudes during neutral conditions while greater dysphoria symptoms were associated with an increase in P2 and P3 mean amplitudes across all affective conditions. Notably, mTBI blast severity was not significantly associated with any examined ERPs. The results demonstrate associations between neural processing of affective images and multiple measures of PTSD symptom severity.

Research Topic: Mental Illness

63. SKY-PACT Dementia Care Model

Possis, Elizabeth [1]; Kavathekar, Rahul [1]; Doane, Bridget [1]; Blondin, Theresa [1]; Atkinson, David [1]; Kemp, Tessa [1]; Mehr, Julie [1]; Tartaro, Caitlin [1]; Velin, Lauren [2]; Cutting, Andrea [1]

1.   Minneapolis VA Health Care System
2.   University of Minnesota

Abstract: Dementia is a common, costly and rapidly growing problem for older Veterans, their families, the VA Health Care System, and society. Dementia severely erodes individuals' functioning and quality of life, creates burden and stress on the entire family, and is a major predictor of institutionalization. Dementia-related costs exceed even those of heart disease and cancer. Given the magnitude of the problem, dementia care should be a priority for Primary Care (PC), but current PC practice cannot accommodate the needs of good quality dementia care. A new model is needed. The Patient Aligned Care Team (PACT) provides the opportunity to design and test a model of dementia care based in PC and aimed at improving the recognition, diagnosis, and management of dementia. Through optimal utilization of PACT members and consultants, our goal is to design a model that: 1) Provides measurable improvement in dementia care quality measures identified in the literature; 2) Is accepted by patients, families and providers; 3) Is scalable to the typical PACT.

Research Topic: Dementia & Neuronal Degeneration

64. Epidemiology of Feeding Tubes in a Veterans' ALS Clinic

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1. Minneapolis VA Health Care System
2. University of Wisconsin, Madison
2. University of Minnesota

Abstract: Objective: Amyotrophic lateral sclerosis (ALS) is a chronic, degenerative neurological disease affecting the brain and spinal cord. Feeding tubes are used to maintain adequate nutrition in patients with dysphagia, upper extremity motor disabilities, and/or hypermetabolic states that may cause malnutrition. This study assessed the epidemiology of feeding tube placement and end of life care in patients with ALS. Methods: A retrospective chart review was conducted of all patients who died between January 2010 and December 2015 who had received care from an ALS Clinic at a single U.S. Veterans Administration (VA) Medical Center. Abstracted data included: date of feeding tube placement (when available), date of initiation of enteral nutrition, survival (from first ALS appointment), location of death, complications related to the tube or feedings, and use of hospice care. Statistics included chi-squared, Mann Whitney U test, and Student's t-test. Results: Of the 139 patients who died with ALS, 88 (63.3%) had received a gastrostomy tube. Tube placement was more common among younger patients, e.g. under 70 years of age. The mean / median time from initial ALS appointment to tube insertion was 247 / 145 days (n = 72). The mean / median survival after feeding tube placement was 352.5 / 258 days (range 4 -2196). The patients with and without tubes did not differ significantly in survival from initial VA ALS Clinic appointment (median 395 vs. 407 days, respectively), location of death, or rate of use of hospice. Conclusion: This VA ALS Clinic had a higher rate of tube placement than reported previously. Use of a feeding tube does not appear affect decisions about enrollment in hospice or location of death. Lack of evidence of a survival benefit associated with use of feeding tubes in ALS in this and prior studies suggests their use should be better targeted to some sub-population(s) of patients with ALS that future research might identify. Further study of quality of life among patients with ALS and a feeding tube may also be needed to justify widespread use of feeding tubes in this population.

Research Topic: Dementia & Neuronal Degeneration
Funding agencies: N/A
Grant support: N/A

65. Steps to Launching a New Program - Creation of the Minneapolis VA Cochlear Implant Program

Rieger, Jerrica [1]; Bryant, Carol [1]

1. Minneapolis VA Health Care System

Abstract: Launching a new service can be an exciting yet challenging endeavor for many professionals. Moving beyond rote thinking is critical to the expandability of any profession. Meeting an identified, previously unmet need that fits the organizational mission and core values gives the program its purpose. This knowledge based poster presentation will review the steps to creating a new program modeled after the newly approved Minneapolis VA Cochlear Implant Program. It is designed to prepare passionate providers to 'take the lead' on establishing or growing an emerging program. This presentation is based off of personal and evidence-based research. The first step in creating a new program is to identify an under-met need that serves an intended population. If the need has not previously been met, there are likely some significant challenges to overcome in order to identify and implement the right set of solutions. Collection of data and progressive thinking will help to overcome considerable challenges, provide rationale for proposed services, and encourage stakeholder buy-in. Development of the infrastructure and business plan can seem daunting at times and out of reach. Team members will need to be engaged from inception to champion efforts and assist with finding solutions to difficult issues. Developing the framework of policies, procedures, financial and human resources, organizational structures, and outreach resources is essential for the program to become established and grow. Once the program is approved by the leadership team, directives are established. This includes training required staff, securing funding, and strategizing a marketing plan. After a program is launched, standard operating procedures (SOP) should be instilled to create efficiency, quality output, and uniformity on complex routine operations. Finally, the program can add value and synergy to other programs by building on strategic relationships and spreading to new target audiences.

Research Topic: Access & Disparities in Care
Funding agencies: N/A
Grant support: N/A

66. The Impact of Agent Orange Exposure on Bladder Cancer

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1.   Minneapolis VA Health Care System

Abstract: The Impact of Agent Orange Exposure on Bladder Cancer Introduction and Objectives: Agent Orange (AO) is a mixture of herbicides used during the Vietnam War to clear forest cover that concealed opposition forces and destroy crops. In 2014, the National Academy of Sciences reported that epidemiologic data was suggestive of an association between bladder cancer and AO exposure, based on evidence that higher levels of exposure are associated with an approximately 2-fold increase in death from bladder cancer. There is little data regarding whether this is due to increased incidence, more aggressive disease or other factors. Additionally, some of the prior data did not account for tobacco use, another potential contributor to bladder cancer carcinogenesis and progression. Methods: Vietnam-era Veterans who had been diagnosed and/or treated for urothelial carcinoma of the bladder (UCB) at the Minneapolis VA Medical Center were identified. We reviewed the medical charts of included patients to examine pathologic stage and grade at diagnosis and identify those who experienced recurrence, progression, cystectomy and death from disease. Patients who left the VA prior to death were censored at the date of their last cystoscopic evaluation. Patients who developed metastatic or muscle invasive bladder cancer were not included further in analysis for recurrence and progression, but only followed beyond this point to determine if death occurred from UCB. Charts were also reviewed for exposure to AO, age and smoking status at the time of diagnosis. Results: 258 patients who met the criteria were identified, with a median follow-up of 44 months. Median age was 66 years (range 44-85). 48% of patients had documented AO exposure based on Veterans Administration registration criteria. The majority of the cohort had high-grade UCB (57%), and 50% had AUA high risk disease at presentation. Recurrence occurred in 120 (46.5%), progression in 36 (14%) and 25 (9.7%) died of disease. AO exposure was associated with high grade disease at presentation on univariate and multivariate analysis when accounting for age and smoking status (OR 2.125; 95% CI 1.264, 3.572; p = 0.004). AO exposure was not significantly associated with stage, recurrence, progression, cystectomy or death from UCB, though low event number likely influenced some of these analyses. Conclusions: In our cohort of Vietnam-era Veterans with UCB, AO exposure was associated with an approximately 2-fold increased risk

Research Topic: Cancer
Funding agencies: N/A
Grant support: N/A

67. Comparative Efficacy Research in Veterans with PTSD (CERV-PTSD)

Schnurr, Paula [1]; Chard, Kathleen [2]; Ruzek, Josef [3]; Curry, Kyle [4]; Petska, Kelly [4]; Sellberg, Courtney [4]

1.   White River Junction VA Medical Center
2.   Cincinnati VA Medical Center
3.   VA Palo Alto Health Care System
4.   Minneapolis VA Health Care System

Abstract: Comparative Effectiveness Research in Veterans with PTSD (CERV-PTSD) is designed to compare efficacy of prolonged exposure (PE) and cognitive processing therapy (CPT). CERV-PTSD is the first direct comparison of these treatments. Eligible participants are randomized to either PE or CPT and receive either treatment with a certified PE or CPT VA-trained therapist. Participants are enrolled in the study for approximately 9 months and receive reimbursement for their time. Study enrollment began in 2014 and ended December 31, 2017. A total of 916 Veterans were randomly assigned to receive either PE or CPT therapy as part of this study at a total of 17 VA sites. The Minneapolis VA has randomized a total of 61 participants (14 women and 47 men). To date, 434 participants have successfully completed the study (31 from Minneapolis).

Research Topic: Mental Illness
Funding agencies: CSR&D
Grant support: VA Cooperative Studies Program (VA CSP)

68. **Treatment with CP2 Attenuates Progressive Amyloid-dependent Degeneration of Noradrenergic Neurons in the APPswe/PS1M146L Mouse Model**

Sheu, Anthony [1]; Gateno, Benjamin [2]; Gallardo, Christopher [1]; Trushina, Eugenia [2]; Lee, Michael [1,3]

1. University of Minnesota
2. Mayo Clinic
3. Minneapolis VA Health Care System

Abstract: Alzheimer's disease (AD) is the most common late onset neurodegenerative disease affecting millions of older adults. Unfortunately, currently approved treatments offer inconsistent symptomatic benefit without delaying the underlying progression of neurodegenerative process. The development of successful therapeutics that can delay or modify AD is of the highest priority for prospective patients, their relatives, and world economy. Previous studies indicate that a brain-penetrant compound, CP2, can activate AMPK and avert the development of AD-like features in three transgenic animal models of AD without significant deleterious effects to normal mice. In this study, we studied whether CP2 treatment of a transgenic mouse model of AD, initiated after the onset of AD-associated symptoms, can attenuate the progression of AD pathology and neurodegeneration. We used a Tg2576/PS1M146L doubly transgenic mouse model where amyloid pathology and cognitive deficits can be seen by 6 months of age. The animals were treated with CP2 starting at 10-12 months of age, for 10-12 months. Our analysis of mouse brains following CP2 treatment shows significant CP2-dependent attenuation of AD pathology, including reduced amyloid deposition. Moreover, CP2 treatment leads to significant reduction in the degeneration of the monoaminergic (MAergic) neurons. Thus, our results show that CP2 has disease-modifying effects in symptomatic animals and provides protection from progressive neurodegeneration.

Research Topic: Dementia & Neuronal Degeneration

69. **Algorithm to Identify Next-Step Pharmacological Antidepressant Strategies among Veterans**

Shiroma, Paulo [1]; Thuras, Paul [1]; Atkinson, David [1]; Baltutis, Eric [1]; Westanmo, Anders [1]

1. Minneapolis VA Health Care System

Abstract: Objective: The 2016 VA/DoD Clinical Practice Guideline for Management of Major Depressive Disorder offer consensus-based recommendations when response to the initial antidepressant medication is suboptimal; however, little is known about 'real-world' pharmacological strategies by providers treating depression in the Veterans Affairs Health Care System (VA Health Care System). Methods: We extracted pharmacy and administrative records from patients with diagnosis of depressive disorder treated at the Minneapolis VA Health Care System between 12/1/2015-11/30/2016. Bipolar disorder, psychosis-spectrum or dementia were excluded. An algorithm using pharmacy data was developed to identify antidepressant strategies: monotherapy (MONO); optimization (OPM); switching (SWT); combination (COM); and augmentation (AUG). Administrative data included demographics, service utilization, diagnosis, and clinical risk for hospitalization and mortality. Results: The sample consists of 863 patients; 14.3% were female; mean age of 51 years. Out of 350 patients who received monotherapy, 60% had an adequate dose. Among 513 patients that underwent a second-step treatment, OPM (66.8%) was the most common strategy, followed by SWT (24.9%), COM (5.8%) and AUG (2.3%). Patients that received COM or AUG had greater proportion of major depressive disorder (MDD), MDD recurrent, and anxiety disorder, and more outpatient visits and higher risk of 90-day and 1-year hospitalization compared to other strategies. Conclusions: This study found that optimizing dosage and switching to another antidepressant are the most common next-step pharmacological strategies used by VA providers, while augmentation and combination are infrequently used strategies. Larger studies are needed to determine whether atypical antipsychotics and other non-antidepressants are potential early options of depression treatment if initial treatment is inadequate.

Research Topic: Mental Illness

70. Risk of Surgical Site Infection Following Carpal Tunnel Release in the Operating Room Versus Clinic-based Procedure Room within a Veterans Affairs Medical Center

Silvis, Amanda J. [1]; Sechriest II, V. Franklin [1]; Gravely, Amy [1]; DeVries, Aaron S. [1]

1.   Minneapolis VA Health Care System

Abstract: OBJECTIVE. A clinic-based procedure room (PR) operating environment is a less restrictive environment compared to the traditional operating room (OR) environment. PRs are increasingly being used for minor surgical procedures. Carpal tunnel release (CTR) is one of the most common surgical procedures in the US Veteran population. It is unknown if there is a difference in the incidence of surgical site infection (SSI) among patients who undergo CTR in the PR versus the OR. DESIGN. Retrospective cohort study. SETTING AND POPULATION. All patients from a single Veterans Affairs Medical Center that underwent clean, elective CTR from October 2014 through April 2017. METHODS. Patient records were queried using Current Procedural Terminology (CPT) codes. Additional demographic and clinical data were obtained through chart extraction. Multivariate logistic regression was used to assess the association between infection and patient demographic characteristics, clinical characteristics, and operating environment. The National Healthcare Safety Network (NHSN) definition for SSI was used. RESULTS. A total of 312 procedures were included in the analysis; 221 procedures in the OR and 91 in the PR. The overall infection rate was 2.88%. After adjusting for covariates, procedure setting was not associated with risk of SSI (p = 0.53; OR= 0.43; 95% CI: 0.03-5.94). Revision CTR of the same wrist after a previous CTR was a significant predictor of SSI (p = 0.02; OR= 28.21; CI: 1.84-434.57). CTR performed in the OR had a similar risk for SSI compared to CTR performed in the PR. The mean total cost of CTR in the OR was $4,254.21 as compared to the PR total cost of $416.93. CONCLUSIONS. The rate of SSI following primary and revision CTR in a US Veteran population was 2.88%, much higher than that reported in non-Veteran populations. Greater emphasis on pre-procedural optimization of key modifiable health risk factors, especially blood glucose control, nutritional status, and body mass index is important. There was no significant difference in rate of SSI between the OR and the PR environments. Revision CTR appears to be higher risk for SSI. Minimally invasive procedures performed in a PR could lead to greater patient satisfaction, access to surgery, higher efficiency, and a 10-fold cost-savings. More facilities should consider the use of PRs for CTR.

Research Topic: Infectious Diseases

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71. VA Traumatic Brain Injury Model Systems: 2018 National Update

Simonson, Adam [1]; Leese, Mira [1]; Finn, Jacob [1]; Lamberty, Gregory [1]

1.   Minneapolis VA Health Care System

Abstract: The Traumatic Brain Injury Model System (TBIMS) program is a prospective, longitudinal, multi-center study which examines TBI recovery and outcomes following coordinated acute medical care and inpatient rehabilitation. The civilian TBIMS has tracked over 13,500 people with TBI for up to 20 years post injury–making it the largest longitudinal TBI database in the United States. In 2008, the Department of Veterans Affairs Polytrauma Rehabilitation Centers (VAPRCs) joined TBIMS and has enrolled over 1,100 active-duty service members and Veterans nationwide who have experienced a mild, moderate or severe TBI. Data collection is progressing and many ongoing projects are currently being conducted within the VA PRC health care system as well in comparison to the civilian TBIMS. In 2015, TBIMS added an additional project titled 'Improved Understanding of Medical and Psychological Needs (I-MaP) in Veterans and Service Members with Chronic TBI'. This new addition not only follows the health conditions and the needs of Veterans, but also the needs of family members or caregivers in relation to their support of the Veteran. Chronic TBI remains an issue in both civilian and Veteran populations and identifying longitudinal effects will contribute to rehabilitation interventions and practice guidelines in VAPRC's.

Research Topic: Acute & Traumatic Injury

72. Pathological role of tau in alpha-synuclein dependent synaptic and memory deficits

Singh, Balvindar [1]; Covelo, Ana [1]; Teravskis, Peter [1]; Benneyworth, Michael [1]; Martinez, Hector M [1]; Liao, Dezhi [1]; Araque, Alfonso [1]; Lee, Michael K [1,2]

1.   University of Minnesota
2.   Minneapolis VA Health Care System

Abstract: Parkinson's disease (PD) is classically characterized by motor dysfunction due to dopaminergic (DA) neuron degeneration in the substantia nigra pars compacta. However, DA-independent, non-motor dysfunction adversely impacts patient quality of life. In particular, cognitive impairment and dementia are prominent disease features. Because mutations in the alpha-synuclein (αS) gene cause familial autosomal dominant PD, αS abnormalities are linked to neuronal dysfunction and neurodegeneration in PD. Further, the current view suggests that cognitive deficits in PD are due to pathological effects of αS abnormalities in forebrain regions. Herein, we show that human missense A53T mutant αS impairs synaptic function, synaptic plasticity, and memory prior to overt neurodegeneration. In particular, while αS is an established modulator of presynaptic neurobiology, we demonstrate that A53T αS uniquely causes cell autonomous deficits in postsynaptic function. Further, mutant αS-induced postsynaptic changes require phosphorylation-dependent tau mislocalization into dendritic spines, leading to AMPA receptor internalization and subsequent impairments in neuronal activity observed both *in vitro* and *ex vivo*. To translate the significance of our findings, we determined whether mutant αS-dependent cognitive deficits in the transgenic mouse model of α-synucleinopathy (TgA53T) require endogenous tau expression. Our results show that the lack of tau expression in TgA53T mice completely blocks the onset of cognitive deficits in this model. Consistent with these behavioral results, *in vitro* dissociated neuronal culture and *ex vivo* hippocampal slice studies show that loss of endogenous tau expression reverses functional deficits caused by mutant αS. In summary, we show that αS abnormalities cause postsynaptic deficits that directly implicate tau as a mediator of αS-induced memory changes.

Research Topic: Dementia & Neuronal Degeneration

73. Automated Eye Tracking For Detection of Blast Brain Injury After a Natural Gas Explosion

Smith, Christina [1]; Abdallah, Tessneem [1]; Bin Zahid, Abdullah [1]; Thorpe, Maxwell [1]; Hoover, Caleb [1]; Warren, Erik [1]; Venkatesh, Shivani [1]; Sturtevant, Dylan [1]; Ahmadi, Aliya [1]; Newgaard, Olivia [1]; Balser, David [2]; Kroll, Rebekah [1]; Samadani, Uzma [2]

1.   Minneapolis Medical Research Foundation
2.   Minneapolis VA Health Care System

Abstract: INTRO: Blast brain injury is difficult to diagnose and treat because it causes neurological damage not generally apparent based on conventional brain imaging and serum/cerebrospinal fluid biomarkers. These injuries have consequences on the overall health of the impacted individual, as well as on the mental, emotional, and cognitive wellbeing of military personal. Ocular motility dysfunction has been noted to have a high incidence in military personnel exposed to blast brain injury. There is currently an overall lack of understanding of the impacts of blast injury on women and children in civilian populations, who may have different susceptibilities to injuries based on their physiological differences. METHODS: A prospective observational study was performed on a total of thirty-six subjects [age (mean ± sd)= 35.6 ± 17.5, range 13-70 years, 23 females] exposed to a natural gas explosion. Subjects were eye-tracked, and the results were compared to age and gender matched controls. Eye tracking consisted of watching a 220 second video travelling in a clockwise aperture on a computer monitor. Subjects also completed a standardized concussion assessment (SCAT3) and underwent clinical vision assessments. RESULTS: Two subjects completed the assessments upon the day of injury, while the remaining survivors were recruited three to nine days after their exposure. The eye-tracking results of the subjects who experienced the blast and enrolled in the study were compared with Wilcoxon-signed rank test to their gender and age matched controls. Five of the eye tracking metrics were found to be statistically different in the exposed subjects. Using logistic regression, the Blast Injury Score (BIS) was developed to analyze the results of the patients located inside of the building during the blast, adjusting for age and gender to predict for the impact of the blast. This BIS showed an AUC of 0.835, sensitivity of 86.4% and specificity of 77.4% distinguishing blast exposed subjects and controls. BIS also was able to discriminate distance from the origin of blast (spearman correlation = 0.731; p-value < 0.001). These results showed an increase in severity for subjects closest to the blast inside the building in comparison to those further away or outside. CONCLUSION: The results of this work indicate a correlation between eye tracking and exposure to blast, and support the use of eye tracking to assess brain injury resulting from blast exposure.

Research Topic: Acute & Traumatic Injury

74. Veterans with Persistent Confirmed Barrett's Esophagus-Associated Low-Grade Dysplasia are at Increased Risk of Progression to High-Grade Dysplasia and Adenocarcinoma

Song, Kevin [1]; Henn, Andrew [1]; Gravely, Amy [2]; Mesa, Hector [2]; Shaukat, Aasma [2]; Hanson, Brian [2]

1.   University of Minnesota
2.   Minneapolis VA Health Care System

Abstract: Background: Studies in the general population have shown that the number of pathologists confirming Barrett's esophagus (BE) associated low grade dysplasia (LGD) is strongly associated with the risk of progression. However, the risk of progression of persistent confirmed LGD (cLGD) has not been well studied in the US population. Aim: To characterize the incidence of progression in persistent confirmed BE-associated LGD in US Veterans. Patients and Methods: All patients with BE and cLGD were identified at Minneapolis Veterans Affairs Health Care System between January 2006 and December 2016. A diagnosis of cLGD was established by consensus of 2 to 7 pathologists including an expert GI pathologist. Information was collected on demographics, past medical history, endoscopic findings, histopathology and lifestyle risk factors. Evidence of persistent cLGD was defined as cLGD on subsequent endoscopy > 3 months after initial diagnosis. The primary endpoint of the study was the development of high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC). Univariate logistic regression analysis was used to assess the association between outcomes and risk factors for progression. A Kaplan-Meier curve was used to evaluate progression-free survival then compared using Log-rank test. Results: Among 72 patients with cLGD, 18 (25%) developed HGD/EAC during a median follow up of 3.17 years (interquartile range, 1.15-5.24). The overall incidence of HGD/EAC in cLGD was 6.96 cases per 100 patient years (95% confidence interval [CI], 4.12-10.99). In patients with persistent cLGD, the incidence of HGD/EAC was 11.59 cases per 100 patient-years (95% CI, 5.99-20.24), and there was an increased risk of malignant progression (odds ratio 5.20; 95% CI, 1.62-16.70). Figure 1 shows the statistical difference in progression-free survival between persistent and non-persistent cLGD (p < 0.001). All patients with neoplastic progression had hiatal hernia (n = 18). Other traditional risk factors including obesity, length of BE, and tobacco use did not show a significant association with progression. Conclusion: Among Veterans, the risk of progression in patient with BE containing persistent cLGD was higher than in those without persistent cLGD. Progression rates for persistent and non-persistent cLGD were 12% and 7% per year, respectively. Regardless of persistence, cLGD progression rates in US Veterans are substantially higher than reported rates in unconfirmed LGD.

Research Topic: Digestive Diseases
Funding agencies: N/A
Grant support: N/A

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75. Contrasting neural networks in mTBI and recovered mTBI Veterans.

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1.   University of Minnesota
2.   Minneapolis VA Health Care System

Abstract: Mild traumatic brain injury (mTBI) is a common injury among Veterans returning from duty, currently effecting 22% of Veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Symptoms following an mTBI such as headaches, fatigue, dizziness and cognitive dysfunction (attention, working memory, verbal learning, etc.) can persist for days or even months. Unfortunately, diagnosis of mTBI still presents challenges due to the diverse nature of the mechanism of injury in mTBI as well as the limited sensitivity of conventional neuroimaging techniques (MRI, CT) in detecting physiological alterations. In this study we evaluate the effect of mTBI on synchronous neural interactions using magnetoencephalography (MEG). MEG is a noninvasive neuroimaging technique that measures magnetic fields produced by postsynaptic potentials in the gray matter of the brain. Compared to conventional neuroimaging techniques, MEG has the capability for more accurate temporal resolution (< 1ms) and spatial localization (2-3mm), which makes it a possible candidate in developing reliable biomarkers for mTBI. Participants were recruited from Minneapolis Veterans Affairs Medical Center and were classified by diagnostic interviews into a current mTBI group or a recovered mTBI group. Results showed a hyper correlation of synchronous neural interactions among Veterans with current mTBI, as opposed to a decorrelation of synchronous neural interactions among the recovered mTBI Veterans. Decorrelation of neural networks has been identified by several investigators as an important component of information processing in the brain by adding neural flexibility to the network. Therefore, a neural network in a hyper correlated state is less available to encode new information. This contrast between the neural networks of mTBI and recovered mTBI Veterans provides the possibility of a valuable biomarker in the diagnosis in mTBI.

Research Topic: Central Nervous System Injuries & Associated Disorders
Funding agencies: N/A
Grant support: Minneapolis VA Health Care System, VA-ORD

76. **Protein Kinase CK2 Promotes Prostate Cancer Cell Survival Under Anti-androgen Therapy Pressure**

Trembley, Janeen [1,2]; Kren, Betsy [1]; Klein, Mark [1,2]; Ahmed, Khalil [1,2]

1.   Minneapolis VA Health Care System   2.   University of Minnesota

Abstract: Introduction: Prostate cancer (PCa) is one of the most prevalent cancers in the aging Veterans population. Prostatectomy is a common therapy for early stage disease; however, frequently the cancer re-emerges as metastatic disease requiring androgen deprivation therapy (ADT). Following its initial regression on ADT, PCa evolves to an androgen-unresponsive state, which is generally fatal within 18 months. Several key therapies for advanced PCa treatment require the presence of and signaling from androgen receptor (AR). CK2 is a protein kinase demonstrating elevated expression and activity in all solid cancers examined. Our extensive work on CK2 in PCa identified numerous essential functions of the kinase including roles in cell growth, proliferation, and suppression of cell death. We have continued our research into PCa disease signaling and therapy response by examining the response of CK2 to androgen deprivation as well as the regulation of AR by CK2. Results: We observed that AR expression is highly downregulated upon loss of CK2 protein and activity. Using castration resistant PCa (CRPC) cells selected for resistance to enzalutamide or abiraterone (agents which target AR), we determined that CK2α, α′ and β mRNA levels were increased slightly when cells were grown in androgen-free compared to standard conditions. Upon examination of CK2α, α′ and β mRNA and protein levels in the enzalutamide and abiraterone-sensitive cells LNCaP (androgen-sensitive PCa) and in C4-2B (CRPC, derived from LNCaP) cells grown under androgen-free compared to standard growth conditions, we noted increased levels of CK2 proteins. Finally, we examined CK2 mRNA and protein levels in LNCaP and C4-2B cells grown under androgen deprivation and treated with enzalutamide or abiraterone. Under these acute treatment conditions, abiraterone increased CK2 mRNA and protein expression in LNCaP as well as increased CK2 proteins in C4-2B. Enzalutamide caused increased CK2 mRNA and protein in C4-2B cells. Conclusions: Our results indicate that one mechanism by which CK2 promotes PCa proliferation is by maintaining AR expression. Increased CK2 expression at both the mRNA and protein level is observed with androgen deprivation, anti-androgen drug treatment, and acquired enzalutamide or abiraterone resistance. We propose that increased CK2 is acting to promote cell survival under conditions of anti-androgen pressure.

Research Topic: Cancer

77. **Medication Treatment for Opioid Use Disorder within the Veterans Health Administration: National Prescribing Trends and Insights from Low-Preforming VHA Facilities**

Valenstein-Mah, Helen [1]; Kenny, Marie [1]; Gordon, Adam [2]; Kay, Chad [3]; Hagedorn, Hildi [1]

1.   Minneapolis VA Health Care System   3.   VA Pharmacy Benefits Management Academic Detailing Service
2.   VA Salt Lake City Health Care System

Abstract: Background: Over 69,000 Veterans in the Veterans Health Administration (VHA) have been diagnosed with an Opioid Use Disorder (OUD). VHA recommends medication (e.g., buprenorphine/naloxone or methadone) as a first-line treatment for OUD and has made substantial efforts to waiver (i.e., certify) providers to prescribe medications for OUD. Despite this, rates of medication treatment for OUD patients within the VHA remains low. Only a minority (35%) of Veterans with OUD receive medication treatment. This poster presents current national trends in OUD medication prescribing among waivered VHA providers as well as results of qualitative interviews from two sites participating in an ongoing implementation trial to increase medication treatment in low-performing VHA facilities. Methods: VHA administrative databases were queried to identify all mental health and non-mental health VHA providers waivered to prescribe medication treatment for OUD as of February, 2018 (n = 2,076). For our implementation trial, we will randomly select 8 low-prescribing (< 21% of OUD patients receiving medication treatment) VHA sites to participate in an intervention to expand access to medication assisted treatment for OUD. Part of the intervention includes interviewing site staff and providers to learn about barriers to expansion of treatment. The first of two sites were interviewed in March 2018 and the results analyzed in preparation for site visits, where training was tailored based to meet the site's unique needs. Results: Most waivered non-mental health providers (84.5%), and almost half of the mental health providers (42.5%) had not prescribed buprenorphine to any patients in the past six months. Of providers that prescribed to at least one patient, both mental health and non-mental health providers prescribed to fewer patients than the allowed 30 patient capacity (22.7 and 13.8 patients on average, respectively). Our qualitative interviews with site staff revealed several barriers to expanding medication treatment for OUD. While there were several barriers common at both sites (e.g., providers' concerns with treating this population) others were unique to a site (e.g., lack of a comprehensive pain clinic). Discussion: VHA providers are prescribing buprenorphine below their waivered capacity. Understanding and addressing patient-, provider-, and system-level barriers is of critical importance to ensure Veterans get effective treatment for OUD.

Research Topic: Substance Abuse

78. Myriocin increases energy expenditure in the animals fed with high fat diet

Wang, ChuanFeng [1,2]; Mavanji, Vijay [2]; Hofmeister, Jacki [1,2]; Grace, Martha [1]; Billington, Charles [1,2]; Kotz, Catherine [1,2]

1. Minneapolis VA Health Care System
2. University of Minnesota

Abstract: BACKGROUND: In our previous studies, high fat diet (HFD) induces hypothalamic neurodegeneration and obesity, and decline of hippocampus dependent memory. The HFD contains high amount of saturate fatty acids such as palmitate. Palmitate *in vitro* reduces neuronal cell viability and increases apoptosis, and application with myriocin (Myr), an antagonist of ceramide de novo synthesis from palmitate, reverses palmitate induced neural apoptosis, associated with decreases in total and individual ceramides. Ceramides are metabolites of saturated fatty acids (e.g. palmitate), and are also shown to reduce viability of neuronal cells *in vitro*. Several reports suggest ceramides influence energy metabolism. In this experiment, we applied myriocin (inhibitor of serine palmitoyltransferase, a key enzyme for ceramide de novo synthesis from palmitate) and amitriptyline (AMT, inhibitor of sphingomyelinase, an enzyme for ceramide release from sphingomyelin) to test if change of ceramide metabolism affects energy balance in the animals fed with high fat diet. METHODS: Male SD rats were fed with low fat diet (LFD) or HFD, and cannulated at lateral ventricle. They were grouped as LFD_Vehicle (Veh), HFD_Veh, HFD_Myr (30 μg), and HFD_Amit (50 μg), with same distribution for body weight and fat mass. They were injected every other day through the lateral ventricle. Energy intake and body weight was measured every other day, and energy expenditure was measured in Sable system. The data were analyzed with SPSS version 24, using general lineal model, and body weight as covariate for energy expenditure. RESULTS: 1) HFD induced obesity (increased energy intake, body weight gain and fat mass) compared to low fat diet. 2) Within HFD subgroups, intervention with myriocin or amitriptyline showed a pattern of decreased body weight gain vs. HFD_Veh rats while their energy intake were similar. 3) For energy expenditure, myriocin treatment increased total energy expenditure, physical activity related energy expenditure, resting metabolic rate and physical activity, and reduced sleeping time. COCLUSIONS: Myriocin increased total energy expenditure, activity related energy expenditure, physical activity, and resting metabolic rate. The measurement for ceramides levels in these rats is in the process. Further experiment will measure energy expenditure with direct injection of ceramide in brain in evaluating effect of ceramide on energy balance.

Research Topic: Other Chronic Diseases

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79. Different phenotypes of feeding response to exercise in young and mature rats

Wang, ChuanFeng [1,2]; Hofmeister, Jacki [2]; Grace, Martha [1]; Billington, Charles [1,2]; Kotz, Catherine [1,2]

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Abstract: BACKGROUND: We study exercise induced feeding change. In preliminary data exercise reduced feeding and body weight (BW) gain in non-naïve adult rats. In a formal test, the exercised naïve young rats showed such sequential feeding pattern: the least, gradual increase, and the most. We performed another experiment in naïve mature rats with same protocol for the young, in comparing and evaluating potential effect of growth phases on feeding responses. METHODS: Young (< 3-m, BW < 400 g) and mature (5-m, BW > 600 g) male rats (each n = 46) were screened in RW, and divided into 4 groups: sedentary (Sed), treadmill (TM, 45 min/day), RW (24/7 access), and Sed with feeding same as RW rats (pair-fed). The term was 37 d for young and 33 d for mature. Feeding, BW gain and fat mass (FM) was measured. RESULTS: 1) Daily feeding in young RW rats was initially decreased, then gradually increased, and finally exceeded others. The feeding in mature RW rats did not exceed others. For cumulated feeding, mature RW rats ate less vs. Sed rats, in contrast to young RW rats. 2) In young rats, RW gained almost 100 g and TM gained about 150 g BW; while the mature RW and TM gained about 20 g and 60 g BW respectively. RW rats in both ages gained the least BW. Mature TM rats had reduced BW gain vs. Sed rats while young TM rats did not. 3) Mature RW rats had negative food efficiency for 3 weeks while young RW rats had positive efficiency all time. RW rats in both ages had the least efficiency. 4) Young RW rats ran > 6 km as mean daily peak and ~ 200 km in 37 days, while matures ran 1.5 km daily and < 30 km in 33 days. 5) All young rats (RW also) increased fat mass, while mature RW rats had little change, and their FM% was reduced. CONCLUSIONS: 1) Exercised young rats always had positive BW gain, while mature RW rats had negative gain most time. 1) Young RW rats ate the most at the end, while mature RW rats did not. 3) Young rats had higher food efficiency vs. mature rats. 4) Young RW rats had higher activity than RW matures. 5) Young RW rats gained fat, while RW matures reduced adiposity. 6) Young and mature rats showed different phenotypes of behavioral response to exercise, possibly because young rats need more energy for physiological growth and high activities, while mature rats need less energy for physiological maintenance and low activity. 7) Mature rats showed considerable exercise induced reduction in feeding, BW and fat mass gain, thus serve as a proper model in future studies.

Research Topic: Other Chronic Diseases

80. Minneapolis VA Evidence-based Synthesis Program (ESP)

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Abstract: Objective: Provide timely and accurate synthesis of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers as they work to improve the health and healthcare of Veterans. Methods: Each of 4 ESP sites prepares 3 systematic reviews each year. Topic nominations come from VA Central Office, VISNs, or individuals in the field (e.g. National Program Directors, Chief Consultants, leaders of VA Task Forces). The reviews are developed using standard methods for development of key questions and scope, identification of included evidence, data extraction, data synthesis, and evaluation of risk of bias and strength of evidence. A Technical Expert Panel is identified for each topic to guide topic development and assist in refining the key questions and scope of the review. Draft reports undergo peer review by content experts and policy partners. Final reports are posted on the VA HSR&D website and disseminated widely throughout VA. Management Briefs and Cyberseminars are key dissemination strategies. Results: For 2017, the Minneapolis VA ESP developed systematic reviews on Existing Measures for Patients with Chronic Pain, Social Determinants of Health for Veterans, and Enhanced Recovery After Surgery (ERAS) Programs for Patients Undergoing Colorectal Surgery. Topics to date for 2018 are: Relationship of Combat-Deployed Mild Traumatic Brain Injury to Post Traumatic Stress Disorder, Depression, Substance Abuse, Anxiety Disorders, and Suicidal Ideation and Adaptive Sports for Disabled Veterans. Conclusions: The Minneapolis VA ESP prepares evidence syntheses on important clinical practice topics relevant to Veterans. These reports help develop clinical policies informed by evidence, lead to the implementation of effective services to improve patient outcomes, and guide the direction for future research to address gaps in clinical knowledge. Funding Source: Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative (QUERI) Key Words: Systematic reviews, evidence-based, Veteran

Research Topic: Health Systems
Funding agencies: HSR&D
Grant support: N/A

81. Evidence for a Novel Regulatory Interaction Involving Cyclin D1, Lipid Droplets, Lipolysis, and Cell Cycle Progression in Hepatocytes

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Abstract: Lipid droplets (LDs) accumulate in hepatocytes as part of the normal response during liver regeneration, but the underlying mechanisms and functional significance of this steatosis are essentially unknown. Here we examine the coordinated regulation of cell cycle progression and LD accumulation. As previously shown, hepatocytes develop increased LD content after mitogen stimulation. Cyclin D1 knockdown and overexpression experiments demonstrated that in addition to regulating proliferation, this cell cycle protein was both necessary and sufficient to promote LD accumulation. Interestingly, cyclin D1 promotes LD accumulation by inhibiting the breakdown of triglyceride by lipolysis, through a mechanism involving decreased autophagy and lipophagy (the degradation of LDs by lysosomal acid lipase). To examine whether inhibition of lipolysis was important for cell cycle progression, we overexpressed adipose triglyceride lipase (ATGL), a key enzyme involved in triglyceride breakdown. As expected, ATGL reduced LD content, but it also markedly inhibited hepatocyte proliferation, suggesting that lipolysis regulates a previously uncharacterized late G1 cell cycle checkpoint. Consistent with this, in mitogen-stimulated cells with siRNA-mediated depletion of cyclin D1 (which inhibits proliferation and stimulates lipolysis), concurrent ATGL knockdown restored progression into S phase. Following 70% partial hepatectomy, a model of robust hepatocyte proliferation *in vivo*, ATGL overexpression led to decreased LD content, cell cycle inhibition, and marked liver injury, further indicating that downregulation of lipolysis is important for normal hepatocyte proliferation. In summary, these studies suggest a new relationship between steatosis and proliferation in hepatocytes: Cyclin D1 inhibits lipolysis resulting in LD accumulation, and suppression of lipolysis is necessary for cell cycle progression.

Research Topic: Digestive Diseases
Funding agencies: NIH
Grant support: R01DK54921 (J.H.A) and R01DK114401, R01DK108790 (D.G.M.)