–Minneapolis VA Health Care System–
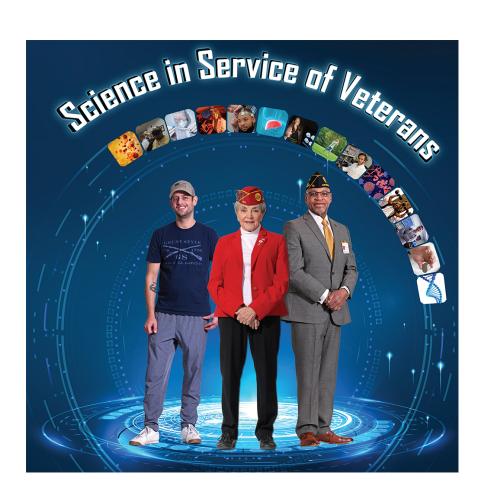# VA Research Day 2022

Program and Abstract List
(alphabetically, by author)

May 10-12, 2022

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

Veterans Health Administration
Office of Research and Development

☆**Program**☆

1. Oral Presentation Session (Tuesday, May 10, 12:00 - 1:30 pm)

12:00 ***The Sex-Dependent Role of Lateral Hypothalamus Orexin Neurons in Learning and Memory***
Brianna Pomonis, Vijaya Mavanji, Catherine Kotz

12:15 ***Provider perceptions of a therapeutically-applied role-playing game***
Alex Curland, Seth Disner, Allison Battles, Thomas Quinlan

12:30 ***Comparison of Comfort and Patient Preference of Common and a Novel Ultrasound-Guided Carpal Tunnel Injection Positions***
Margaret Crosby, David Balser, Willis Schuerger, Kersten Schwanz, Alexander Senk, Luke Walters, Sarah Weyrauch, Corey Wheelock

12:45 ***Graded Motor Imagery for Persons with Amputations: A Scoping Review***
Kierra Falbo, Hannah Phelan, Dawn Hackman, Rebecca Vogsland, Tonya Rich

1:00 ***Arouse, Don't Awaken: Treating Trauma-Related Nightmares with a Wearable Device***
Nicholas Davenport, Mary Evans-Lindquist, Rebecca Hiltner, Christopher Prementine, J. Kent Werner

2. Keynote Session (Thursday, May 12, 12:00 - 1:30 pm)

☆**Introductions and Welcome**... Hanna E. Bloomfield, MD, MPH
Associate Chief of Staff, Research Service

☆**2022 Lederle Award Presentation**...Timothy Wilt, MD

Recipient:
Dimitri Drekonja, MD, MS
"Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men With Urinary Tract Infection: A Randomized Clinical Trial"

JAMA. 2021;326(4):324-331.

☆**Keynote Address** ....**Kristine E. Ensrud, MD, MPH**
Professor, Medicine and Epidemiology & Community Health, University of Minnesota
Staff Physician, General Internal Medicine, Minneapolis VA Health Care System

"A Research and Mentoring Career Journey: Lessons Learned Along the Way"

3. Poster Session (Thursday, May 12, 2:00 - 4:00 pm)

Oral Presentations: Author Index *(first author only)*

Poster Presentations: Author Index *(first author only)*

Oral Presentations

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1. **Comparison of Comfort and Patient Preference of Common and a Novel Ultrasound-Guided Carpal Tunnel Injection Positions**

Crosby, Margaret [1]; Balser, David [1]; Schuerger, Willis [1]; Schwanz, Kersten [1]; Senk, Alexander [2]; Walters, Luke [1]; Weyrauch, Sarah [1]; Wheelock, Corey [3]

1. University of Minnesota
2. Minneapolis VA Health Care System
3. Schwab Rehabilitation Hospital and Care Network

Abstract: Ultrasound-guided corticosteroid injections can provide relief for those suffering from carpal tunnel syndrome (CTS). This requires patients to hold positions that expose the volar aspect of the wrist for an ulnar approach injection. Sustaining these positions can aggravate CTS symptoms and cause discomfort elsewhere. This may result in the patient moving or requiring a position adjustment intraprocedure increasing the chance of prolonging the intervention and complication including injury to surrounding structures. This study aimed to compare levels of discomfort among three positions for ultrasound-guided carpal tunnel injections. Veterans referred for EMG evaluation of CTS at the Minneapolis VA EMG clinics were eligible for the study; a total of 30 participants were evaluated. Participants were asked to hold 3 different positions (hypersupination, airplane, and reclined-rotated) with the opposite wrist for 10 minutes each. Participants rated their pain level, ease of performing and holding each position, exacerbation of underlying symptoms, and position preference. Results were analyzed with a two-way repeated measures ANOVA. The hypersupination position was determined to be the least preferred and most painful position to hold, demonstrating a statistically significant increase in pain scores compared to airplane and reclined-rotated, which were not significantly different from one another. When performing CT injections, patient comfort can be optimized by avoiding hypersupination of the wrist and opting for a position like airplane or relaxed-reclined which provide similar exposure for ulnar approach injections while inducing lower levels of discomfort.

Research Topic: Rehabilitative Medicine
Funding agencies: N/A
Grant support: N/A

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2. **Provider perceptions of a therapeutically-applied role-playing game**

Curland, Alex [1]; Disner, Seth [1-2]; Battles, Allison [1]; Quinlan, Thomas [1]

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

Abstract: Role-playing games can provide opportunities for interactive, collaborative experiences, which can be applied therapeutically. Therapeutically-applied role-playing games (TA-RPGs) provide opportunities to gain insight into interpersonal and intrapersonal dynamics, build relationships, and enhance various skills. A TA-RPG group for Veterans, called Roll for Recovery (RfR), has been implemented within the Minneapolis VA and utilizes Dungeons & Dragons. As a novel intervention, providers may be unfamiliar with TA-RPGs and may result in fewer referrals for care. A survey was developed to examine provider perceptions and attitudes towards RfR. Results from this survey will improve outreach efforts, and determine which providers most likely to refer Veterans to RfR. The survey was completed by 53 Minneapolis VA providers (mean age of 41 [SD=9.2]; 33 identified as women, 18 men, 1 Non-Binary/Other identity, 1 preferred not to say). Amongst respondents, psychologists were most represented (n=25). Of those surveyed, 26 providers had not referred a Veteran to RfR, while 27 providers had either previously discussed the group with a Veteran or referred. Qualitative data was collected on providers' perceptions of RfR, familiarity with therapeutic gaming, perceptions of barriers to referral and participation, potential benefits. Thematic analysis was used to identify themes of responses to free-response questions. Common themes included issues related to logistics of participating, technology, and perceptions Veterans could improve coping skills and social relationships. There were no differences found in likelihood to refer related to gender or familiarity with gaming. However, older providers were more likely to have discussed or referred to the group, b=0.08, SE=0.04, p=0.029. Providers endorsing perceiving logistical barriers for Veteran participation were less likely to have referred, t(51)=-2.38, p=0.021. Strategies to increase access to the group include providing reminders of group time, technological assistance, and increasing accessibility of platforms such as Webex on VA devices. Group facilitators can convey the group's purpose, typical session content, and individual outcomes to providers through flyers, videos of mock sessions, and presentations to providers using data from the group. Additionally, promotional materials can be developed to provide sample questions to assess fit for group, referral process, and facilitator contact information.

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

3.   Arouse, Don't Awaken: Treating Trauma-Related Nightmares with a Wearable Device

Davenport, Nicholas [1]; Evans-Lindquist, Mary [1]; Hiltner, Rebecca [1]; Prementine, Christopher [1]; Werner, J. Kent [2]

1.   Minneapolis VA Health Care System   2.   Uniformed Services University

Abstract: Introduction: Nightmares are common among combat-exposed Service Members and Veterans, especially those with a history of Post-Traumatic Stress Disorder (PTSD). The persistent experience of trauma-related nightmares is associated with reduced quality of life and comorbid mental health conditions. Few validated treatment options are available, and the most commonly prescribed medications include undesirable side effects and have limited demonstrated efficacy. A more direct intervention, in the form of a wearable device that interrupts distressing dreams, may provide an effective alternative for Veterans with chronic trauma-related nightmares. Methods: A sham-controlled, double blind randomized control trial (RCT) was conducted to test the efficacy of a wearable device designed to monitor physiological signs (e.g., heart rate, movement) during sleep and provide tactile stimulation (i.e., haptic feedback) to interrupt signs of distress without full wakening. A total of 72 Veterans with frequent self-reported nightmares, poor sleep quality (Pittsburgh Sleep Quality Index [PSQI] >9), and history of PTSD were enrolled in this 30-day trial. Measures of sleep quality and mental health were collected at baseline and approximately every 7 days thereafter. Participants were randomly assigned to receive either the Active device or a Sham device that performs all functions except providing stimulation. Primary measures of sleep quality and PTSD symptomatology were the PSQI and PTSD Checklist (PCL-5), respectively. Results: Both conditions were associated with significant within-person improvement on all measures tested, and while the Active condition generally had numerically stronger improvement than Sham, these differences were not statistically significant. However, when considering only participants who used the device on more than 50% of nights (N=20 Active, 26 Sham), the Active condition was associated with significantly greater improvement, compared to Sham, on the PSQI (4.4 vs. 1.7; t=2.81, p=0.007) and a study-specific Likert scale of nightmare severity (6.4 vs. 2.7; t=3.47, p=0.001). Conclusions: There is preliminary evidence that a wearable device can provide improved sleep for Veterans reporting frequent trauma-related nightmares. Given the burden of medications on both the Veteran and clinician, the availability of a non-invasive digital therapeutic option may provide substantial improvement in Veteran health and fewer clinical resources.

4.   Graded Motor Imagery for Persons with Amputations: A Scoping Review

Falbo, Kierra [1-2]; Phelan, Hannah [3]; Hackman, Dawn [2]; Vogsland, Rebecca [1]; Rich, Tonya [1-2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota
3.   Medical College of Wisconsin

Abstract: Phantom limb pain (PLP) is complex and multifactorial, making treatment difficult for rehabilitation clinicians. Graded motor imagery (GMI) is a non-pharmacological treatment that aims to reduce pain by addressing cortical reorganization, theorized to cause PLP, and consists of three stages: limb laterality, motor imagery, and mirror therapy. The objective of this review was to explore and describe the evidence of the full GMI protocol for PLP following amputation. A scoping review was conducted according to the JBI framework and was reported following the Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Reviews. Works were included if the design involved one or more stages of GMI for participants over 18 with PLP following amputation. Extracted data included study characteristics, participant demographics, amputation information, characteristics of GMI, and outcomes. Data were examined for similarities in participants, methods, and other study characteristics. Of 1344 works screened, 38 studies, representing 17 countries, met our inclusion criteria. Most were uncontrolled before and after studies (53%). Participants were primarily men, and many works did not report race or ethnicity (84%). Most included individuals with unilateral amputations (89%) with lower limb levels in 45% of works, upper limb in 32%, and both in 21%. Cause of amputation was non-dysvascular in 32%, dysvascular in 3%, both in 24%, and not reported in 42%. Time since amputation was over one year in 26%, less than one year in 3%, and both in 29%, with no range reported in 32%. GMI involved mainly mirror therapy (76%) and one GMI stage (84%). The most measured outcome was PLP intensity (95%). Most authors (82%) reported positive results following GMI intervention. Despite success of the full GMI protocol in other pain populations, research on GMI for PLP after amputation has focused on mirror therapy. No standardization exists for the most effective characteristics of GMI in the PLP population. Demographics of study participants varied greatly with much unreported, making comparisons between study results difficult. Further work should evaluate effects of the full GMI intervention in this population and examine the patient characteristics most appropriate for this treatment. The represented countries indicate that GMI for PLP has been implemented internationally, so future work could have a widespread impact.

5.   **The Sex-Dependent Role of Lateral Hypothalamus Orexin Neurons in Learning and Memory**

Pomonis, Brianna [1-2]; Mavanji, Vijaya [1-2]; Kotz, Catherine [1-2]

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

Abstract: Lateral hypothalamus (LH) orexin neurons are implicated in energy expenditure, feeding, and cognition. Earlier studies showed that orexin dysfunction impairs memory in orexin-ataxin mice, and that female mice have higher expression levels of LH orexin receptors. Based on these findings, we hypothesized firstly, that stimulation of orexin neurons improves cognitive function in mice; secondly, that orexin stimulation would decrease body weight and food intake; and lastly, that female mice are more sensitive to the memory-enhancing effect of orexin. We manipulated orexin tone by chemogenic activation of LH orexin neurons in 18-mo.-old orexin-cre mice (n=8). Mice were prepared with a stimulatory designer receptors exclusively activated by designer drugs (DREADD) virus in the LH, recovered for 3 weeks to allow virus transfection, and randomly assigned to saline or clozapine N-oxide (CNO, DREADD activator) treatment. Mice were then trained for cognitive testing using Barnes maze, contextual object recognition (CORT), and two-way active avoidance (TWAA). Following training, mice received CNO or saline and were tested for learning and memory 24 hours later. In a separate study, food and body weight were recorded 48 hours after treatment. Orexin activation improved cognitive performance without significantly changing food intake or body weight, suggesting these cognitive changes are not dependent on changes in energy metabolism. Improvement on different tests after orexin stimulation suggest types of cognition enhanced by orexin varies by sex, and warrants further investigation.

Research Topic: Obesity
Funding agencies: VA BLRD; NIH
Grant support: I01BX003004; I01BX003687; R01DK100281

Poster Presentations

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

Adabag, Selcuk [1]; Diem, Susan [1]; Hill, Debra [1]; Donaire, Marti [1]; Kantorowicz, Alexandra [1]; Johnson, Debra [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 Objective & Key Results (OKRs) include; enhance 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, Co-Director, Associate Director-Operations, Operations Manager, Quality Assurance Manager/Clinical Research Nurse, and Enrollment Manager/Administrator 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 ñ 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 investigators and coordinators; Created procedures for mobile recruiting at CBOCs; Work stream meetings on improving study design & procedures; Creation of Work groups to develop and beta test 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; Creation of VA CSP-NODES Executive Board; Creation of CSP Studies Toolbox to facilitate NODES and Non-NODES VA sites in study implementation; Facilitated remote working for our local CSP study coordinators and research assistants in response to the pandemic; Contributed to numerous manuscripts in peer-reviewed journals; Contributed, participated, and won national 2020 CSP Shark Tank competition for NODES Mobile Recruiting Units; Attended national Own The Moment training and facilitated TMS course creation and training for local study coordinators and research associates; Implemented a Hub-and-Spoke model to facilitate VA CSP research at other facilities within VISN23; and Members of a VA CSP-NODES Work group (ACCESS) in order to provide rural Veterans the opportunity to participate in VA CSP research studies.

Research Topic: Health Care Delivery
Funding agencies: VA CSRD
Grant support: VA CSP

2.   Revascularization of Hibernating Myocardium and Effects on Diastolic Function and Fibrosis

Aggarwal, Rishav [1-2]; Qi, Steven [1-2]; So, Simon [1-2]; Reyes, Christina [1-2]; Rose, Rebecca [1-2]; Wright, Christin [1-2]; Nixon, Joshua [1-2]; McFalls, Edward [3]; Butterick, Tammy [1-2]; Kelly, Rosemary [1-2]

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

Abstract: Objective: This study uses porcine model to investigate mechanisms of diastolic dysfunction in hibernating myocardium (HM) and recovery with coronary artery bypass surgery (CABG). Methods: HM was induced in Yorkshire-Landrace female juvenile swine (n=30) by placing a c-constrictor on left anterior descending (LAD) artery causing stenosis without infarction. At 12 weeks, animals developed HM phenotype and were either sacrificed (HIB group; n=11) or underwent CABG with 4 weeks recovery (HIB + CABG group; n=19). Control group was matched for weight, age, and gender to the HIB. Prior to sacrifice, cardiac Magnetic Resonance Imaging (MRI) was done at rest and low dose dobutamine infusion. Tissue was obtained for histologic and proinflammatory biomarker analysis. Results: Cardiac MRI confirmed preserved global function in all groups. Diastolic peak filling rate (PFR) was lower in HIB (5.4±0.7 vs. 6.7±1.4 respectively) (p=0.002) compared to control, and partial recovery toward control with CABG (6.3±0.8) (p=0.06). Histology showed interstitial fibrosis in endomysium in HM compared to normal myocardium, which persisted post-CABG. Alpha-smooth muscle actin (SMA) stain identified increased myofibroblasts in HM that decreased post-CABG. Cytokine studies in HM showed decreased PGC1a expression but increased expression of GM-CSF and NFκB. Following CABG, PGC1a and NFκB expression returned to control while GM-CSF, TNFα, and IFN. remained increased. Conclusion: In porcine model of HM, NFκB signaling mechanisms were associated with increased myocardial fibrosis that along with PGC1a expression, recovered with CABG. However, diastolic dysfunction in HM at increased workload persists despite CABG, suggesting a need for additional adjuvant therapies at the time of revascularization.

Research Topic: Basic Sciences

3.   Variation in Reporting of Incidental Findings on Lung Cancer Screening and Association with Subsequent Assessment

Atoma, Bethlehem [1]; Fabbrini, Angela [1]; Clothier, Barbara [1]; Campbell, Megan [1]; Melzer, Anne [1]

1.   Minneapolis VA Health Care System

Abstract: The presence of incidental findings (IFs) on low-dose CT (LDCT) for lung cancer screening (LCS) generates workload. The association between how IFs are reported and subsequent evaluation is not well understood. We quantified the distribution, frequency and clinical significance of IFs on LDCT and the association of report characteristics with subsequent assessment. Retrospective chart review of patients undergoing initial LCS at the Minneapolis VA (2015-2018). IFs were any non-nodule findings in the LDCT report and considered potentially significant (SIFs) if they were expected to require follow-up. Category "S" is the Lung-RADS code applied when a SIF is present. Primary outcome was follow-up, defined as any assessment ordered and/or completed in relation to the finding, or documented to be unnecessary. High- risk SIFs were defined as potentially malignant. Outcomes were analyzed using a mixed effects model with individual patient as a random effect. Patients (n=901) were primarily male (94.1%) and current smokers (62.1%). IFs were common (93.9%). Pulmonary findings (48.6%) were most common. 34.2% of IF were considered significant. 7.4% were high-risk and 28.2% had workups ordered, completed, or documented to be unnecessary, of which 13.2% completed additional evaluation. A minority of SIFs (37.2%) had "S" applied to the LDCT. Reporting of IFs varied greatly by Radiologist. Despite not applying "S" category, radiologists frequently recommended testing. Presence of a radiologist recommendation (OR 3.3, 95% CI 1.9-5.7), high-risk finding (OR 2.9, 95%CI 1.5-5.6), and reporting in the impression (OR 2.1 95%CI 1.2-3.8) were associated with increased odds of workup, while "S" code, number of IFs, presence of a suspicious pulmonary nodule, reading radiologist, and patient age were not associated with odds of workup. IFs are extremely common on LDCT and may be clinically significant, but are not reported systematically. Reporting characteristics have large impacts on subsequent evaluation. Guidance and training to support structured reporting of SIFs may improve this process, with the goal of generating appropriate testing when needed and preventing low-value care.

Research Topic: Respiration & Pulmonary Disease

4.   **The novel orexin agonist RTIOXA-47 reduces body weight and fat mass in New Zealand Obese Mice**

Benefato, Izabelle [1]; Pomonis, Bri [2]; Mavanji, Vijaya [3]; Shekels, Laurie [3]; Zhang, Yanan [4]; Kotz, Catherine [2-3]

1.   Universidade Federal de São Paulo
2.   University of Minnesota
3.   Minneapolis VA Health Care System
4.   Research Triangle Institute International

Abstract: Stimulation of energy expenditure (EE) is a common strategy in obesity treatment, and EE has several components, including that derived from spontaneous physical activity (SPA), which produces non-exercise activity thermogenesis (NEAT). The neuropeptide orexin A increases SPA and NEAT in several animal models. The New Zealand Obese (NZO) mouse is a polygenic animal model of obesity and diabetes, but orexin action in these mice has not been examined. Our aim was to evaluate the potential therapeutic effect of a novel orexin agonist (RTIOXA-47) for the treatment of obesity in NZO mice. We hypothesized that peripheral RTIOXA-47 administration increases SPA and attenuates obesity in NZO mice. To test this, male and female C57BL/6 WT and NZO mice (n=24) were housed individually and randomly assigned to treatment with saline or RTIOXA47 (40 mg/kg), administered via intraperitoneal injection 5 days per week for five weeks. The current n=3 per species, sex and treatment, but an additional cohort is in progress. Body weight (BW) and food intake (FI) were recorded weekly. Body composition (BC) and 24-hour SPA and EE were measured before and after treatment. To analyze the data, Generalized Estimated Equations (GEE) were performed followed by Bonferroni post hoc test. Significance was set at p=0.05. A significant sex*strain*time*treatment interaction was observed for BW, FI, SPA, EE and fat mass (FM). Significant sex differences were seen in both NZO vs. WT across all variables. A benefit of RTIOXA-47 was seen in WT males and NZO females as both sets of treated mice had significantly lower BW and FM compared with their respective non-treated group at study's end (p<0.05). For FI, the same was observed, but only in WT females (treated < non-treated). These preliminary findings suggest that RTIOXA47 may help reduce BW and FM, but additional statistical power gained by inclusion of the next cohort of mice will help expand and solidify these results.

Research Topic: Obesity

5.   **All of Us Research Program**

Billeadeau, Taylor [1]; Lee, Gregory [1]; Sharif, Nawshin [1]; Klein, Mark [1-2]

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

Abstract: Background: The main goal of the All of Us Research Program is to build on the Precision Medicine Initiative which aims to consider how genes, the environment, and a person's lifestyle might impact their health. The program aims to collect and study data (including clinical data and "panomics") from 1 million or more people living in the United States. Unlike a single research study focused on a specific disease or population, All of Us will serve as a national research resource to inform thousands of studies, covering a wide variety of health conditions affecting many different people. The program especially puts emphasis on including populations that have historically been underrepresented in biomedical research. Participants will have opportunities over many years to provide data about themselves that will help researchers learn more about how individual differences in lifestyle, environment, and biological make-up can influence health and disease. Methods: To achieve the goal of creating a research cohort of 1 million or more U.S. participants, the NIH has engaged a number of organizations to establish the infrastructure of the All of Us Research Program. The key program components include a Data and Research Center, a Participant Technology Systems Center, Participant Center, a Biobank, and a number of Health Care Provider Organizations (HPO). The VA is a core HPO, and the Minneapolis VA Healthcare System is one of the first wave of VA sites to open for enrollment. NIH and VA have a goal to have approximately 100,000 Veterans enroll in the All of Us and MVP studies simultaneously for comparison. Enrollment Activities: Once a participant indicates interest, participants are scheduled for an appointment. At the study visit, participants learn about the program (including data security), provide consent, answer surveys electronically, and have 8 tubes of blood plus one urine sample collected. Samples are sent to the Biobank (run by Mayo Medical Laboratories). Participants also have the opportunity to view some of their genetic results, including ancestry, traits and health-related results. As of April 18th, 2022, the All of Us Research Program has enrolled 332,659 total core participants nationally and 1215 core participants at the Minneapolis VA. Conclusion: The All of Us Research Program will provide a national panomics resource and lay a scientific foundation for Precision Medicine.

Research Topic: Genomics

6.   **AW-Shift! Visualizing Pressure Distribution for Wheelchair Users and Their Clinicians Anywhere, Anytime**

Bornstein, A. Soleil [1]; Wacek, Amber [1]; Truty, Timothy [1]; Kemmer, Sara [1]; Fairhurst, Stuart [1]; Brown, Rebecca [1]; Anderson, Michelle [1]; Hicks, Brandon [1]; Stein, Crystal [1]; Eddy, Byron [1]; Goldish, Gary [1]; Gravely, Amy [1]; Barrett, Benjamin [1]; Hansen, Andrew [1]; Morrow, Melissa [2]; Vos-Draper, Tamara [3]; Olney, Christine [1]

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

Abstract: The potential for developing a pressure injury is a persistent and lifelong risk for wheelchair users with a spinal cord injury or other conditions that limit movement and sensory function. Although seating specialists prescribe regular weight shifts for offloading the seated area and redistribution of pressure, evidence tells us that weight shift routines are difficult for the wheelchair user to maintain in the real-world environment. Currently clinicians must rely on patient self-report and personal observation during short clinic visits to understand the wheelchair users seating behaviors. Relying on this limited information has contributed to failed education strategies and poor outcome improvements. To respond to the problem, our multi-institutional, multi-disciplinary team (Minneapolis Adaptive Design & Engineering [MADE] Program at the Minneapolis VA Health Care System, University of Minnesota, and Mayo Clinic) developed a system that acquires data from a pressure map placed between the wheelchair user and the wheelchair cushion. The associated app provides real-time, continuous data to the wheelchair user about how well pressure is distributed, reminders for weight shifts, and alerts for unexpected pressure changes. This mobile app can also transmit the data to a server, where the wheelchair user's clinician can be given access to view trended data on a clinical dashboard web app. The research team set up iterative virtual focus groups with Veterans with spinal cord injury (n=7) and clinicians (n=6) to expand the software and product development for both the user and clinician interface. During the next phase of this project, in-patient wheelchair users (n=6) will now have access to data through an intuitive and compelling user interface, substituting their lack of sensation for real time visualization of their seated pressure distribution. Therapists will be able to review short term and long-term progress toward individualized weight shift goals and trends in weight shift performance through the clinical dashboard. We hypothesize that access to these data will facilitate improved educational conversations between clinicians and patients to optimize individualized weight distribution management.

Research Topic: Preventive Medicine
Funding agencies: VA RRD
Grant support: RX003222

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7.   **Women Veterans in VA Research**

Buelt-Gebhardt, Melissa [1]; Kantorowicz, Alexandra [1]; Hill, Debra [1]; Danan, Elisheva [1]; Adabag, Selcuk [1]

1.   Minneapolis VA Health Care System

Abstract: Women Veterans have historically been underrepresented in VA clinical trials, despite being the fastest growing subpopulation using the Veterans Health Administration. Over half a million women Veterans received health care in the VA in FY19, a 237% increase from the year 2000. To provide women Veterans with patient-centered, evidence-based care, we need attention to sex and gender in scientific research; findings from research done solely on men cannot necessarily be safely generalized to women. Acquiring the evidence to optimize patient-centered care for women Veterans requires equitable inclusion of women in VA research. However, it can be challenging to recruit sufficient women Veteran study participants. Despite their growing numbers, women remain an extreme numerical minority, accounting for less than 10% of VA patients. In addition to their minority status, women's underrepresentation in VA research can also be attributed to factors such as mistrust in VA, women's unique healthcare needs, VA eligibility, and sociodemographic differences from men. For example, today's women Veterans are on average younger, are more racially diverse, have more caregiving responsibilities, and have less social support than male Veterans. To address these factors, enhanced recruitment techniques aimed at increasing participation of women Veterans in research studies are being developed. Inclusion of women in VA clinical trials in sufficient numbers to enable sex and/or gender-based analyses of treatment outcomes will improve the real-world care of women Veterans.

Research Topic: Women's Health
Funding agencies: VA CSRD
Grant support: Cooperative Studies Program

8. **The effects of the nicotinic acetylcholine receptor agonists, anatabine and nornicotine, on energy balance in rats depends on sex and diet type.**

Bunney, Patricia [1]; Mavanji, Vijay [1]; Shekels, Laurie [1]; Grace, Martha [1]; Kotz, Catherine [1]

1.   Minneapolis VA Health Care System

Abstract: Significance: The two minor tobacco alkaloids (MTAs) anatabine (ANAT) and nornicotine (NORNIC), are found in low levels in tobacco products and activate nicotinic acetylecholine receptors (nAChRs) within the brain. Their effects on energy balance and low addictive potential make them good candidates for obesity pharmacotherapy. We hypothesized that MTA administration could prevent weight gain, with differences between male and female rats and varying as a function of diet type. Method: Study 1: we administered saline, ANAT or NORNIC for 4 weeks to male and female rats (n=8-10 per group) on chow diet. Study 2: we administered saline or ANAT for 4wks to male and female rats on diets varying in fat and sucrose content (n=8-10 per group). Studies were conducted in metabolic cages (Sable Promethion); food intake (FI), weight gain, body composition, physical activity (PA), and energy expenditure (EE) were measured. Results: Study 1: ANAT and NORNIC slowed weight gain and reduced fat mass (p<0.01) in both males and females. Both MTAs reduced FI in males (p<0.05), whereas only ANAT reduced FI in females (p<0.05). The MTAs increased PA (p<0.01) in both sexes, with NORNIC effects lasting longer. Both MTAs increased EE in males, while only ANAT increased EE in females (p<0.01). Females were more sensitive to MTA effects on PA and EE (p<0.05). Study 2: ANAT administration prevented weight gain, and reduced FI and body fat in males on low fat/low sucrose and low fat/high sucrose diets, with diminished effects in males on high fat/high sucrose diets. In contrast, ANAT had no effect on weight gain, fat mass, or FI in females on any diet tested. Conclusion: These results demonstrate that the nAChR agonists NORNIC and ANAT effects are dependent on sex and diet type.

Research Topic: Obesity

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9. **Comparing Socket Casting Techniques on Comfort and Time: Implications for New Prosthetists**

Cave, Juan [1]; Muschler, Katherine [1]; Looft, John [1]; Hansen, Andrew [1]; Cutti, Andrea [2]; Fatone, Stefania [3]

1.   Minneapolis VA Health Care System
2.   INAIL-Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro
3.   University of Washington

Abstract: Socket casting for persons with lower-limb amputations has been virtually unchanged for decades. Casting is traditionally performed by a prosthetist manually applying pressure to the seated patient's plaster wrapped limb to get an accurate shape. The cast is then filled with plaster and modified to a shape that evenly distributes pressure over the residual limb while wearing the socket. During hand casting it can be experience-dependent to achieve the even pressure distribution needed to ensure a comfortable socket. A relatively new casting technique allows patients to stand in a pressurized water cylinder while the plaster cast is taken to obtain the shape of the residual limb (Symphonie Aqua System, Romedis). Allowing the patient's body weight to be applied to the residual limb during casting may improve their comfort by more evenly distributing pressure in the final socket. This study compares hand casting to water casting on Socket Comfort Score (SCS), time taken to cast, and time taken to modify the cast. During the study visits two experienced prosthetists took both a hand and water cast of the subject. Two of those casts were then modified and made into check sockets, which were fit on the subject. Each procedure was timed, and SCS was recorded on a 10-point scale before any modifications were made. Preliminary results from 7 Veteran subjects with transtibial amputations show that sockets made using hand casting had an average initial SCS of 7.14 and sockets made with the Symphonie had an average initial SCS of 7.71. The average time to cast with the Symphonie was 22 minutes for Prosthetist 1and 24 minutes for Prosthetist 2. The average hand casting time was 7 minutes for Prosthetist 1 and 9 minutes for Prosthetist 2. Modifying the casts was performed only by Prosthetist 1. Prosthetist 1 took an average of 13 minutes to modify the water casts and 25 minutes to modify the hand casts. Water casting took longer to cast, but less time to modify, while the hand casting technique was quicker to cast, but longer to modify. When combined total time spent casting and modifying was 32:01 minutes for the hand cast and 35:24 minutes for the water casts. Time and patient comfort are important factors a new practitioner must take into consideration when determining which technique to select. Proper education and accommodation to either technique must be acquired prior to being clinically implemented.

Research Topic: Prosthetics

10. Associations Between Agent Orange Exposure and Alzheimer's Disease Neuropathology in Veterans

Chan, Kayla [1]; McCarten, J. Riley [2]; Fairhurst, Catherine [2]; Dykoski, Richard [2]; Clark, H. Brent [1]; Hemmy, Laura [2]

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

Abstract: Exposure to Agent Orange (AO), a toxic herbicide used during the Vietnam War, has been associated with adverse health outcomes. AO exposure is linked with Lewy-body based neurodegenerative disease, but it is unclear whether it also leads to increased risk for Alzheimer's disease (AD). Previous studies have examined the clinical diagnosis of AD and all cause dementias, but no studies have investigated AO exposure's association with the neuropathological diagnosis or characterization of AD. In this study autopsy report generated data from 328 Vietnam era Veterans who received an autopsy at the Minneapolis VAHCS between 2005-2020 were examined for an association between AO exposure and neuropathological diagnosis of AD. AO exposure was recorded from the medical record and neuropathological diagnosis of AD and the presence of neurofibrillary tangle (NFT) accumulation (yes/no) were extracted from autopsy reports. Veterans exposed to AO (n=92) had a mean age of 66.7 (SD 5.8) at death, 100% were male, and 83% were white. Those not exposed to AO (n=236) had a mean age of 65.6 (SD 6.9) at death, 98% were male, and 75% were white. Demographic differences were non-significant. Results from chi-square tests for independence showed there was no significant association between AO exposure and either AD diagnosis or the presence/absence of NFT. This suggests that the relationship between AO exposure and neurodegeneration may be limited to Lewy-body diseases, or that the relationship between AO exposure and AD depends on factors like exposure duration or intensity. Limitations of this sample are the dichotomous nature of the variables, and the relative youth of the sample. It may be that an association between AO exposure and AD neurodegeneration may only be apparent in an older sample in which neurodegeneration would be further progressed, or when AD neurodegeneration is measured with greater granularity. Overall, although an association between AO exposure and neuropathological diagnosis of AD was not found, further investigation of the effects of AO on dementia and neurodegenerative diseases remains vital to provide appropriate compensation to Veterans and to better understand risk for neurodegenerative diseases.

Research Topic: Alzheimer's Disease
Funding agencies: N/A
Grant support: N/A

11. Gulf War Illness: C-Reactive Protein is Associated with Reduction of the Volume of Hippocampus and Decreased Fractional Anisotropy of the Fornix

Christova, Peka [1]; James, Lisa [1]; Carpenter, Adam [1]; Lewis, Scott [1]; Johnson, Rachel [1]; Engdahl, Brian [1]; Georgopoulos, Apostolos [1]

1.   Minneapolis VA Health Care System

Abstract: Memory and mood impairments are among the most commonly reported symptoms in veterans with Gulf War Illness (GWI), suggesting hippocampal involvement. Several studies have also documented evidence of inflammation in GWI. The aim of the present study was to evaluate the association between C-reactive protein (CRP), a marker of inflammation, and hippocampal volume and microstructural alterations of its major output, the fornix. Sixty-three veterans with GWI provided blood samples for evaluation of CRP and underwent a 3T magnetic resonance imaging scan from which hippocampal volume and fornix fractional anisotropy (FA) were obtained. Results demonstrated that CRP was significantly and negatively associated with hippocampal volume and fornix FA in GWI. Given the known closely interwoven associations between inflammation and neurodegeneration, it is possible that the effects we observed could be due to neurodegeneration, secondary to chronic neuroinflammation. Finally, given the known association of hippocampus to memory and mood disorders, our findings provide new insights into memory and mood alterations associated with GWI.

Research Topic: Gulf War Veterans
Funding agencies: N/A
Grant support: N/A

12. **Evidence of shifting healthcare costs from non-VA payors to VA Community Care (CC): Chart review and survey of Veterans receiving CC cardiology referrals for heart failure**

Diem, Susan [1]; Cutting, Andrea [1]; Ensrud, Kristine [1]; Bart, Bradley [1]; Ni, Orly [1]; Taylor, Brent [1]; Duan-Porter, Wei [1]

1.   Minneapolis VA Health Care System

Abstract: BACKGROUND: The MISSION Act of 2018 expanded Veteran eligibility to receive healthcare provided by community facilities and paid for by VA (Community Care, or CC). Whether Veterans are shifting costs for specialty care of complex chronic conditions such as heart failure (HF)in the community from non-VA payors to VA is unknown. METHODS: We prospectively identified all Veterans referred for outpatient CC cardiology care for HF in VISN 23 from 7/20-9/6/2020, using consult titles and ICD10 codes on consult requests. We included only the first eligible referral if there were multiple. We mailed a survey to eligible Veterans on a rolling basis; if >15 eligible Veterans were identified in a given week, we randomly selected 15 to mail the survey. The survey addressed aspects of HF care, including whether participants had received cardiology care from non-VA providers within the previous 2 years, and if so, who paid for that care. We excluded referrals that were subsequently discontinued. 85 Veterans were sent surveys and included in this analysis. Two physicians reviewed VA medical records for the 85 Veterans, examining them for evidence of cost-shifting community HF cardiology care to the VA from non-VA payors. The CC referral was classified as cost-shifting if 1) the referral was the first CC cardiology referral or a re-authorization of a CC cardiology referral initiated since June 2019 (MISSION Act implementation) and 2) notes in the medical record indicated that the Veteran had previously received this care in the community not paid for by VA. Discrepancies in classification between reviewers were resolved by consensus. RESULTS: Of the 85 referrals, 25 (29%) were classified as shifting the cost of community cardiology care from another payor to the VA since June 2019. Sixty (70%) Veterans responded to the survey; 20 of the 25 Veterans classified as cost-shifting responded - 10 reported Medicare, 2 reported private insurance, and 3 reported both Medicare and private insurance had previously paid for their community cardiology care. CONCLUSION: In this cohort of Veterans referred for CC cardiology care for HF, a substantial proportion (29%) had previously received non-VA HF care paid for by non-VA payors and and were shifting the costs of that care to VA-paid CC since MISSION Act implementation. Future research to confirm the extent of this cost-shifting for HF and other costly chronic medical conditions will be important for policymakers.

13. **Acoustic Classification of Early and Advanced Osteoarthritis of the Knee in Clinical Settings**

Draisey, Ashley [1]; Nichols, Chris [2]; Goktug, Ozmen [2]; Fairhurst, Stuart [3]; Voss, Greg [3]; Hansen, Andrew [3]; Inan, Omer [2]; Ewart, Dave [3]

1.   Abbott Northwestern Hospital
2.   Georgia Institute of Technology
3.   Minneapolis VA Health Care System

Abstract: Background: Knee osteoarthritis (OA) is a prevalent and debilitating disease. The human knee generates noise, termed crepitus, in states of health and OA. Knee acoustic emissions are quantitatively different in knees with advanced, radiographic OA (rad-OA) than from healthy control knees in limited, controlled settings. The ability to use acoustics to identify early, pre-radiographic OA (pre-OA) or to detect any knee OA in environments with background noise, such as a clinic, has not been tested. Purpose: Our primary objective is to differentiate knees with pre-OA and rad-OA from healthy control knees using knee acoustic emissions measured with a wearable device in a clinical setting and while performing scripted maneuvers. Methods: This was a single center study comparing acoustic data between healthy, pre-OA, or rad-OA knees from 27 subjects (37 knees,14 healthy, 11 pre-OA, 11 rad-OA). Pre-OA was defined by x-rays findings of Kellgren-Lawrence (KG) grade 1 or KG 0 with MRI findings of cartilage damage. Rad-OA was defined as KG 2 or greater. Age, BMI, gender, and knee symptoms measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS) were recorded. Patient characteristics were compared with statistical methods (gender with chi-square, KOOS scores between pre-OA and rad-OA with paired t-tests, age and BMI using ANOVA with Tukey's post-hoc). Acoustic data was collected in rheumatology clinic exam rooms using accelerometers attached to the patient's knee during scripted maneuvers: flexion-extension, sit-to-stand, and walking. Acoustic data were processed, and their variability and patterns visualized with unsupervised machine learning. Acoustic features were used to train a linear-classification algorithm for knee disease status using supervised machine learning. Accuracy of our classification algorithm was measured with Leave-One-Out Cross-Validation. Results: The rad-OA disease group was older than the control group (mean age 62 vs 37, p=0.005). There were no other between group differences in subject characteristics. In knees with rad-OA, our classification algorithm was highly accurate in classifying disease state during flexion-extension (accuracy 90%, area under the curve (AUC) 0.94) and sit-to-stand (100%) maneuvers. Walking was slightly less accurate (81%, AUC 0.75). Accuracy for pre-OA was similar (80% flexion-extension, 88% sit-to-stand, 84% walking). Accuracy was higher when analyzing the three scripted maneuvers combined than with each individual maneuver (rad-OA 92%, AUC 0.99, pre-OA 95%, AUC 0.97). Acoustics were more accurate for disease status classification than age, BMI, and KOOS score. Conclusion: Our study illustrates the efficacy and potential utility of using acoustic emission

analysis to accurately identify presence of early and advanced osteoarthritis of the knee in clinical settings with limited control of background noise.

Research Topic: Arthritis
Funding agencies: VA RRD
Grant support: VA RRD

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14. Assessment for the Safety, Tolerability, and Effectiveness of Rifapentine given Daily for LTBI (ASTERoiD)

Drekonja, Dimitri [1]; Amundson, Carla [1]

1. Minneapolis VA Health Care System

Abstract: The primary objectives of this open-label Phase III clinical trial are to compare the safety and effectiveness of a six week regimen of daily rifapentine (6wP, the experimental arm) with a comparator arm of 12-16 weeks of rifamycin-based treatment of latent M. tuberculosis infection (LTBI). We hypothesize that the safety and effectiveness of 6wP is non-inferior to a comparator arm of 12-16 weeks of rifamycin-based treatment of LTBI. The comparator arm's regimens will include 12 weeks of once-weekly isoniazid (INH) + rifapentine (3HP), 12 weeks of daily INH + rifampin (3HR), and 16 weeks of daily rifampin (4R). Although tuberculosis is an uncommon disease among veterans, it's contagiousness makes it a public health priority, and current treatments are long and onerous for veterans to take, especially since some treatments interact with other medications. This trial will be conducted among veterans who are at increased risk of progression to active TB and require treatment of LTBI. The first primary endpoint is safety, which will be measured by drug discontinuation due to adverse drug reaction (ADR) associated with 6wP and the rifamycin-based comparator arm (3HP, 3HR, or 4R). If safe, effectiveness will be assessed, measured by progression to culture-confirmed active tuberculosis infection.

Research Topic: Infectious Diseases
Funding agencies: N/A
Grant support: U.S. Centers for Disease Control and Prevention; Tuberculosis Trials Consortium; IAA 20FED2000031PSE -003-01

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15. Identifying Root Causes of Gender-Diverse Patient Care Inequity: A Quality Improvement Approach

Fairbairn, Elizabeth [1]; Goldsmith, Elizabeth [2]

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

Abstract: VHA directives require gender-affirming care for transgender and gender-diverse patients. A health services survey of transgender Veterans was conducted at the Minneapolis VA in July 2020. Of those surveyed, 29% did not completely agree that their provider provided gender-related care that is affirming, and 44% did not completely agree that their provider was knowledgeable about gender-related care. We set out to identify root causes for this gap in patient experience through a quality improvement approach by gathering information about Women's Comprehensive Care Clinic processes, observing clinic processes, and engaging with care team members through a clinic-wide feedback form and informal interviews. This information was organized into a process map and fishbone diagrams to identify opportunities for intervention to improve transgender and gender-diverse patient experience s. The root causes identified were related to people (clinical staff), processes, and the electronic medical record. Opportunities for improvement among clinical staff included knowledge of gender-affirming care specifics and experience with caring for gender-diverse patients. There is a lack of clinical processes in place to consistently identify gender-diverse patients' used names, gender when different from birth sex, and medically relevant changes to anatomy and/or sex hormones. These clinic processes are intimately linked with, and at times limited by, the electronic medical record. By identifying these root causes and presenting them, we hope to inspire quality improvement interventions to close the gap and successfully 'provide clinically appropriate, comprehensive, Veteran-centered care with respect and dignity to enrolled or otherwise eligible transgender' Veterans (VHA Directive 1341(2)).

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

16. AFOCE: Comparative Effect of Commercially Available Custom Dynamic Orthoses

Falbo, Kierra [1-2]; Comstock, Brogan [1-2]; Cave, Juan [1]; Wacek, Amber [1]; Sauerbrey, Matthew [1]; Looft, John [1-2]; Hansen, Andrew [1-2]; Hendershot, Bradford [3]; Wilken, Jason [4]

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

Abstract: Traumatic lower limb injuries can lead to poor long-lasting health outcomes such as decreased physical mobility, increased rates of depression, and decreased quality of life. The goal of this multi-site clinical trial is to identify how the form, fit, and function of two commercially available carbon fiber dynamic ankle foot orthoses (CDOs), the Reaktiv and PhatBrace, influence outcomes after injury. We hypothesized that each CDO would result in an improvement of function relative to no device. Our secondary hypothesis states that each CDO design will result in significant differences across the various outcome measures. Veterans between the ages of 18 and 65 are recruited to participate if they have experienced a lower limb injury over two years ago with remaining symptoms, such as ankle pain or muscle weakness. Participants are asked to complete baseline data with no device and follow-up data after three months use of each CDO. Data collection includes mental health surveys, physical outcome measures, gait analysis, qualitative feedback, and preference on devices. Gait analysis data is collected using a 20-camera Qualisys motion capture system. Two male Veterans have completed the study to date in Minneapolis. Preliminary results show differences in peak ankle dorsiflexion, torque, and power for both devices compared to not wearing a CDO. Additionally, comparing the two devices shows a potential difference in ankle torque and power. Both participants preferred wearing a CDO compared to no device. One participant preferred the Reaktiv, citing a greater reduction in ankle pain and improved durability. The other participant preferred the PhatBrace due to the reduced bulk and ease of fitting clothing over the device. In these two participants, CDOs improved physical function and reduced ankle pain. These data may influence the understanding of how CDO use may positively affect physical function, mental health, and overall quality of life after traumatic lower limb injuries. Data collection is ongoing to add to the understanding of the effects of these CDOs with additional participants.

Research Topic: Rehabilitative Medicine

17. VA Women's Stranger Harassment Patient Feedback Project

Farley, Tracy [1]; Duran, Alisa [1]; Mann, Katelyn [1]; O'Brien, Emma [1]; Cannon, Ashley [1]; Schamberger, Stacy [1]; Danan, Elisheva [1]

1. Minneapolis VA Health Care System

Abstract: Background: Stranger harassment has been a persistent issue for women veterans who obtain care in the VA Healthcare System. Previous VA research found that 25% of women Veterans who are routine users of VA primary care reported inappropriate or unwanted comments or behaviors by male Veterans on VA grounds. Methods: To track efforts to end harassment, the VA Women's Health Practice Based Research Network systematically collected brief, anonymous surveys from women Veterans seen in VA primary care and/or women's health clinics. The Minneapolis VA Women's Comprehensive Care Clinic has participated in 5 survey waves since 2017, with 4 years of quantitative data available for review. During each wave, Women's Clinic MSAs distributed 100 single-page questionnaires to a convenience sample of women Veterans over a 1-2 week period, with response rates of 100% (2017), 26% (2018), 94% (2019), and 97% (2021). Veterans were also asked to provide free text responses to questions about how to improve their VA experience. Results: The proportion of women at the Minneapolis VA who reported that they strongly agreed with the statement 'As a woman, I feel welcome at the VA' increased from 54% in 2017 to 77% in 2021. The proportion who reported experiencing harassment dropped from 44% in 2017, to 14% in 2021, paralleling national trends. In 2021, harassment was usually attributed to male Veterans (70-85%), and less commonly to VA staff members (39-45%), though VA staff only rarely tried to help (11-16%). In free text responses, women Veterans provided positive feedback about their experiences at the Minneapolis VA, and also cited room for improvement in: acknowledging women Veterans, providing more services and staff for Women's healthcare, and respect during Check-In/Check-Out. Conclusion: Women veterans often experience harassment when they come to the VA for medical care, though rates of harassment are decreasing in recent years. Local findings from this Veteran feedback project have been presented to Minneapolis VA leadership, and national findings have been used to support efforts to prevent harassment through culture change campaigns, to intervene using system-wide bystander trainings, and to respond and support those who have experienced harassment.

Research Topic: Women's Health

18. **Neutrophil-to-Lymphocyte Ratio in Patients with Primary Non-Melanoma Skin Cancer is Not Predictive for Development of Secondary Non-Melanoma Skin Cancers**

Fulk, Travis [1-2]; Westanmo, Anders [1]; Gravely, Amy [1]; Gupta, Rachit [3]; Ravishankar, Adarsh [1-2]; Goldfarb, Noah [1-2]

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

Abstract: Neutrophil-lymphocyte ratio (NLR) is a cost-effective marker derived from a complete blood count (CBC) with prognostic implications for numerous malignancies. An elevated NLR portends a worse prognosis for several malignancies, including malignant melanoma and Merkel cell carcinoma, but a decreased NLR was found for non-melanoma skin cancer (NMSC). Our group previously found that a lower NLR was associated with an increased risk for secondary (2°) NMSCs in a small study. This study aims to further investigate the relationship between NLR and 2° NMSCs after a primary (1°) NMSC diagnosis in a large population. This retrospective cohort study included data from patients in the Minneapolis Veterans Affairs Health Care System with a 1° NMSC diagnosis between January 1, 1999 and December 31, 2016, who also had a CBC with differential between 30 days before to 60 days after the diagnosis date. Exclusion criteria were missing age, sex, or NMSC diagnosis date, prior diagnosis of leukemia, myelodysplastic or myeloproliferative disease, or a CBC with differential performed within two weeks of an inpatient or emergency department encounter. Data was collected on age, sex, race, tobacco use, transplant history, non-steroidal anti-inflammatory drug and/or aspirin use between three months before to three years after 1° NMSC diagnosis, and date, type, and anatomic location of 1° NMSC and 2° NMSC, if applicable. Primary study outcomes were mean NLR between 30 days before to 60 days after 1° NMSC diagnosis for patients with or without a 2° NMSC within three years (patients are followed for a minimum of three years after a 1° NMSC diagnosis at our institution) and time to 2° NMSC stratified by NLR <4 versus =4. The results were analyzed using Pearson's chi squared test, the two-sample T-test, and unadjusted survival analysis by high (=4) versus low (<4) NLR. Statistical analysis used SAS version 9.4 (SAS institute, Cary NC) and statistical significance was set at $p < 0.05$. The results of this larger population study showed no statistically significant difference in mean NLR between patients with and without 2° NMSC within three years of diagnosis of a 1° NMSC (3.76vs.3.78; p=0.9311). We also did not find any statistically significant difference in time to 2° NMSC within three years for those with high (=4) versus low (<4) NLR (Hazard Ratio=0.896+/-0.742; p=0.2552). In summary, we found no prognostic value for NLR in determining risk for 2° NMSC following diagnosis of 1° NMSC.

19. **Inter-prosthetist variability in determining sock ply for appropriate socket fit**

Gibney, Marion [1]; Falbo, Kierra [1]; Bornstein, Soleil [1]; Hansen, Andrew [1]

1. Minneapolis VA Health Care System

Abstract: Despite the longstanding use of prosthetic socks, differences in prosthetists' determinations of appropriate sock ply for a proper socket fit has not been examined. This project aims to collect information about inter-prosthetist variability regarding the use of prosthetic socks to fine-tune socket fit. Certified prosthetists met with patient models with transtibial amputations to determine how many ply of socks the models should use for an appropriate socket fit. A specialized toolkit with several 1-, 3-, and 5-ply socks, as well as a supply of silicone, was available for use. Steps taken by each participant were noted during patient model interactions and coded for analysis. Preliminary analysis includes mode, average sock ply, and range of socks used for each patient model interaction. Sock ply determinations ranged from 0- to 5-ply, demonstrating the variation between prosthetists' in determining the sock ply needed for an appropriate socket fit. A range of 5-ply demonstrates that prosthetists' final determinations of appropriate socket fit fall within one sock of each other. There is no 'gold standard' to guide prosthetists in determining how many socks should be used for an appropriate socket fit. Socket fit is decided by the prosthetist for each patient, and prosthetic sock management is taught to patients to help them ensure a continued proper fit when they leave the clinic. Results from this project can inform us about prosthetists' use of socks and help start to set a baseline for variability in the use of these socks among prosthetists. This project sets the groundwork to determine a baseline for inter-prosthetist variability regarding the use of prosthetic socks. This project can be repeated in different clinics to help other prosthetists determine average sock ply variability there how variable its prosthetists are in their use of socks. While a range of 5 ply can be managed with one sock, it is possible that prosthetists find this difference to be too much. Further steps can be taken to determine how many ply prosthetists find acceptable. If results from this project can be extrapolated to a greater number of prosthetists, it is possible that variability in socket fit that can be managed with one additional sock. This is good news for patients whose prosthetists encourage the use of socks for fine-tuning socket fit over the course of a day.

20. Combined tDCS and Cognitive Training for Mild Cognitive Impairment and Early Clinical Alzheimer's Type Dementia

Gilmore, Casey [1]; McCarten, J. Riley [1]; Lim, Kelvin [1]; Hemmy, Laura [1]

1.   Minneapolis VA Health Care System

Abstract: There are currently no disease-modifying treatments for cognitive and behavioral symptoms associated with early clinical Alzheimer's disease (AD), and only minimally effective symptomatic treatments are available. This study uses a transcranial direct current stimulation (tDCS) augmented executive functioning training intervention to target cognition and brain circuits that are impaired in patients with mild cognitive impairment (MCI) and early AD. The goal is to improve cognitive performance and functional outcomes in patients with MCI and early AD. Methods: This study aims to recruit 50 Veterans with MCI or early AD who are receiving outpatient services in the Geriatric Research, Education, and Clinical Center (GRECC) Memory Loss Clinic. This study is a double-blind, randomized, placebo (sham) controlled study. Participants are randomly assigned to receive either active or sham tDCS, both paired with cognitive training tasks. Ten sessions of training/tDCS sessions (20 minutes of 2mA current stimulation with 45 minutes of cognitive training tasks) occur over 2-3 weeks, performed at the participant's home. Participants attend an enrollment and training session prior to study intervention, and follow-up sessions at 3 weeks and 3 and 6 months after study initiation. Results: So far, one participant (79 yo male) has successfully completed the at-home tDCS/cognitive training sessions and the 3 month follow-up. Clinical Relevance: Executive cognitive impairments in patients with MCI or early AD have been associated with poor decision-making ability and lack of insight, potentially leading to compromised job performance, financial mismanagement, increased personal safety risk, relationship stress, and poor medical treatment adherence. While disproportionate memory impairment is a hallmark of both conditions, there are compensatory strategies available to reduce disability associated with very early stage memory impairment in those who are otherwise cognitively intact. Compensatory strategies are much less effective for executive dysfunction, as the disability itself impairs one's ability to recognize when such strategies are needed and successfully employ them. Novel, well-tolerated, neuroplasticity-based interventions that can reduce executive impairment by targeting both cognitive control (an executive ability) and its underlying neural dysfunction are needed to improve cognitive outcomes, safety, and quality of life for patients with MCI or early AD.

Research Topic: Alzheimer's Disease
Funding agencies: N/A
Grant support: N/A

21. Multimodal Characterization of Suicide Risk in Veteran Inpatients

Gilmore, Casey [1]; Yu, Carol [1]; Lim, Kelvin [1]

1.   Minneapolis VA Health Care System

Abstract: Previous research has found that the four weeks after discharge from inpatient care is one of the highest risk periods for suicidal behavior, primarily due to poor post-discharge treatment use (nearly 65% of Veterans do not attend planned therapy after discharge). It is vital to identify ways to reduce suicidal thoughts and behavior, and to increase help-seeking and connection to suicide prevention resources to prevent Veteran suicides in general and during the post-discharge period. The overarching aim of this study is to examine the impact of multiple factors (cognitive, psychophysiological, clinical, psychosocial) on Veterans' help-seeking and suicide risk during the high-risk transition period from inpatient to outpatient care. Research Plan and Methods: This pilot study assesses the feasibility of performing a multimodal assessment of factors associated with suicidal behavior in the 1K inpatient psychiatric unit. Thirty-eight Veteran inpatients in the 1K Psychiatric unit will be recruited. We will collect measures representing multiple domains related to suicidal ideation and behavior, including executive function cognitive performance, resting and stimulus-induced brain activity using electroencephalography (EEG), and self-report measures of impulsivity, suicidal ideation and behavior, and help seeking. These measures will be collected during their inpatient stay, as well as at 2 weeks and 4 weeks following discharge. Additionally, Ecological Momentary Assessment (EMA) will be collected twice daily throughout the 4 week follow-up period, allowing repeated sampling of participants' behaviors and experiences in real time. Clinical Relevance: Reducing Veteran suicide has been the top clinical priority of the VA for the last few years. However, the total number of suicides among Veterans has continued to increase. There is a critical need for targeted treatments to reduce the risk of suicide in Veterans. Previous research has shown that the transition from inpatient to outpatient care, including the four weeks after discharge from inpatient care is one of the highest risk periods. Understanding the factors affecting suicidal thoughts and behaviors during this period will help guide future rehabilitative and treatment approaches.

Research Topic: Suicide Prevention
Funding agencies: N/A
Grant support: N/A

22. Effects of Neuromodulation and Cognitive Training for Suicide in Veterans: The ENACTS study

Gilmore, Casey [1]; Yu, Carol [1]; Thuras, Paul [1]; Lim, Kelvin [1]

1.   Minneapolis VA Health Care System

Abstract: Impaired executive function, such as impaired decision making and impulsivity, has been identified as an important contributor to the transition from suicidal ideation to suicide attempt. To address the epidemic of Veteran suicide, we will test the feasibility, acceptability, and preliminary effectiveness of a five day transcranial direct current stimulation (tDCS) augmented executive functioning training intervention. This intervention will be delivered to inpatients who have been admitted to the 1K psychiatric unit and deemed to be at heightened suicide risk. The ultimate goal is to reduce future suicide events (ideation, attempts, deaths) and improve quality of life (e.g. social relationships, health resource utilization). Methods: We will test feasibility and acceptability of a five day intervention of ten sessions of tDCS augmented executive function training in a high suicide risk population. Inpatients have the highest risk of suicide attempts within the initial weeks following discharge, suggesting that this could be a critical intervention period. 38 Veteran inpatients in the 1K Psychiatric unit will be recruited. The five day intervention will be delivered during inpatient stay, prior to discharge. We will collect measures representing multiple domains related to suicidal ideation and behavior, including executive function cognitive performance, and self-report measures of impulsivity, suicidal ideation and behavior, and help seeking. These measures will also be collected at 1 month and 2 months following discharge. Additionally, we will collect longitudinal and daily real-time data on help-seeking, suicide risk, and related factors in the month after discharge using Ecological Momentary Assessment (EMA). Clinical Relevance: Reducing Veteran suicide is a top clinical priority of the VA. However, the number of suicides among Veterans has continued to increase. There is a critical need for targeted treatments to reduce the risk of suicide in Veterans. The transition from inpatient to outpatient care, including the four weeks after discharge, is one of the highest risk periods. The low cost, simplicity, and safety of this intervention makes it easy to deliver and scale to clinical settings. If this pilot trial is successful, it would set the stage for a larger trial to test the effectiveness of this intervention for reducing suicide events in a high suicide risk population, and help guide future rehabilitative and treatment approaches.

23. Brain signatures during the course of emergence from the unresponsive wakeful/vegetative state after severe brain injury

Gilmore, Casey [1]; Peterson, Michelle [1]; Mortimer, Diane [1]; Pellizzer, Giuseppe [1]

1.   Minneapolis VA Health Care System

Abstract: Severe brain injury causes disorders of consciousness (DOC). The assessment of DOC patients relies primarily on observed motor output. However, this assessment is often challenging due to the sensory, motor and cognitive impairments resulting from the brain injury. This issue is particularly critical since the diagnosis and prognosis has important ethical and medical consequences in regard to the selection of care, treatment, and end-of-life decisions. Consequently, families of DOC participants often struggle in making long-term decisions, and an alternative methodology could help them in this process. We are currently investigating the use of electroencephalography (EEG) in assisting with the assessment of DOC patients. We recorded EEG during resting state and during an auditory oddball paradigm in one patient with DOC admitted in the Minneapolis VA Emerging Consciousness Program. The Coma Recovery Scale-revised was used to rate the state of consciousness of the patient. In addition, the EEG of ten control participants was also recorded during resting state and the auditory oddball paradigm. The control participants had a history of severe brain injury and loss of consciousness for at least 24 hours following the injury before emerging. We found that the EEG power spectrum of the DOC patient during resting state developed a prominent beta frequency (about 20 Hz) peak during the process of emergence from the unresponsive wakeful/vegetative state state. This profile of the power spectrum contrasts with the profile of the power spectrum during the prior unresponsive wakeful/vegetative state state, as well as with the profile of the emerged brain-lesioned controls. The occurrence of the prominent beta frequency peak preceded also the differentiation of the P300 event-related potential in the auditory oddball paradigm which is considered to be an indicator of conscious perception. We believe that EEG has the potential to provide objective information that can assist with the assessment of DOC patients. In particular, the development of a prominent beta-frequency peak seems to coincide with the improvement in level of consciousness, and may precede the occurrence of conscious perception.

24. Barriers and facilitators of evidence-based psychotherapies for chronic pain: A systematic review

Goldsmith, Elizabeth [1-2]; Ullman, Kristen [1]; Miller, Wendy [1-2]; Landsteiner, Adreinne [1]; Stroebel, Benjamin [3]; Hill, Jessica [1]; Ackland, Princess [1-2]; Wilt, Timothy [1-2]; Duan-Porter, Wei [1-2]

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

Abstract: Background: Chronic pain conditions are common causes of disability in the United States and are associated with psychological distress. Currently recommended first-line evidence-based psychotherapies (EBPs) for chronic pain include cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), and mindfulness-based stress reduction (MBSR). To help identify key gaps for future research on implementation of EBPs for chronic pain, we completed an evidence review on barriers, facilitators, and evaluations of implementation strategies for CBT, ACT and MBSR. Methods: We searched MEDLINE, Embase, PsycINFO, and CINAHL from inception through March 2021 for English-language articles addressing barriers, facilitators and/or implementation strategies for eligible EBPs used to treat chronic pain. Two reviewers screened abstracts, conducted full-text review using pre-specified criteria, independently assessed quality of studies, and independently abstracted quantitative and qualitative data. We conducted best-fit framework qualitative synthesis of results. Results: 20 eligible studies addressed barriers and facilitators for uptake of CBT (n=13), ACT (n=4) and MBSR (n=5) for chronic pain. Two studies examined more than one EBP. 14 were conducted in the US, with 6 in the Veterans Health Administration (VHA). 19 studies were rated moderate or high quality. Only one eligible study addressed implementation strategies. Common barriers to uptake included mismatch between patients' pain-related beliefs and perceptions of core therapy concepts. Barriers specific to CBT included cultural and communication factors, while those for MBSR included physical discomfort. Shared facilitators included positive patient-therapist or patient-group dynamics. Additional CBT facilitators included patient readiness for change and telehealth availability. Patient demographics were inconsistently assessed and did not consistently predict EBP attendance. Conclusions: Eligible studies focused largely on patient-level barriers and facilitators, with little provider- or system-level information. Recommendations for future research include (1) using comprehensive frameworks to examine provider-and system-level barriers and facilitators in clinical practice settings; (2) identifying patient-level factors contributing to heterogeneity of treatment effects and uptake; and (3) rigorously evaluating outcomes for implementation strategies used to increase uptake of EBPs for chronic pain.

Research Topic: Pain

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25. Characteristic Determinants of Survival after Feeding Tube Placement in Amyotrophic Lateral Sclerosis

Greenwood, Daniel [1]; Tiryaki, Ezgi [1]

1. Minneapolis VA Health Care System

Abstract: Background: Amyotrophic Lateral Sclerosis (ALS) was established as a military service-connected disorder in 2009. During the disease course, 10-29% of individuals in the United States have a feeding tube placed. These percentages are greater when patients see a dedicated nutrition support team (56%) or when patients have bulbar onset (78%). Weight loss and malnutrition shorten survival, while obesity and maintenance of an obese body mass index (BMI) are associated with longer survival. The aim of this study was to determine if there are relationships between respiratory function, weight, BMI, physical function, dysphagia, dysarthria, age, form of disease onset and survival after feeding tube placement for the patient with ALS. Methods: This was a retrospective chart review study. Veterans who received specialty ALS care at an ALS Center of Excellence between January 1, 2010, and January 1, 2020 were screened for inclusion. Data extraction was completed utilizing a data abstraction tool within CPRS. A priori alpha was set at=0.05. Findings: 222 patients met inclusion criteria, 215 were male (97%), and 7 were female (3%). The median age at the time of initiation of care was 69 years. Limb onset was the most prevalent form of disease onset (72%) versus bulbar onset (28%). The majority, 58% of patients had a feeding tube placed during their disease course. For patients with bulbar onset, 83% had a feeding tube placed. The mean weight loss during the time of follow-up was 5.4% of total body weight. Twenty-eight percent of patients met diagnosis criteria for malnutrition, and 71% of patients experienced dysphagia. Rate of decline in BMI (p<0.01), weight (p<0.01), and ALSFRS-R (p=0.04), as well as older age (p<0.01), were all significantly associated with shorter survival. Patients with bulbar onset and a feeding tube lived significantly longer than patients with limb onset and a feeding tube (median=310 versus 223 days, p<0.01). Class I obesity demonstrated longer survival (p<0.01). ALSFRS-R <39 and forced vital capacity <75 at the initial visit were both predictors of shorter survival (p<0.01). Interpretation: Consistent with other research, rate of decline of BMI, weight, and ALSFRS-R, as well as older age were associated with shorter survival, while obesity was associated with longer survival. Individuals with older age, rapid decline in ALSFRS-R, weight, and BMI, where significant losses have already occurred, may not benefit from a feeding tube.

Research Topic: Nutrition

26. Using a Learning Health Systems Approach to Improve Cervical Cancer Screening in VA

Groebner, Rhonda [1]; Danan, Elisheva [1]; Bruesehoff, Michele [1]; Finnigan, Jill [1]; Pestka, Deborah [1]; Duran, Alisa [1]; Das, Kamalini [1]

1.   Minneapolis VA Health Care System

Abstract: Background: Adoption of evidence-based management for abnormal cervical cancer screening results has been inconsistent. In 2019, the VA Office of the Inspector General found that 48% of 42 facilities inspected were non-compliant with VA requirements for timely notification and tracking of abnormal Pap test results. A learning health system is one in which data generated from practice are coupled with external evidence to produce knowledge that can improve care and efficiency. As part of a VISN 23 strategic initiative award, this project is using a learning health system framework to implement a Pap Hub and Spoke Model to centralize and standardize follow-up of screening results. Method: Prior to Pap Hub implementation, we conducted a mixed-methods, multilevel stakeholder needs assessment with care team members and leadership across VISN 23. Primary care providers received a request to complete a web-based questionnaire. We conducted semi-structured virtual group interviews with women's health leadership and navigators at 7 sites in the VISN (6 Spoke sites and Minneapolis). We also performed a retrospective chart review of baseline screening results management 3 months pre-implementation. Results: Among 55 primary care providers surveyed, 91% perform 5 or fewer cervical cancer screening tests per month, and most providers (75%) supported the creation of a Pap Hub. Across 7 sites interviewed, there was broad variation in existing processes and concerns related to results notification and tracking. Identified barriers to Pap Hub implementation included concerns about sustainability, reluctance to remove follow-up responsibility from primary care providers, and a desire to see a demonstration of the Pap Hub process. Potential facilitators included an interest in automated normal response letters, a desire for real-time expert consultation, and staffing limitations that would be alleviated by re-allocating follow-up responsibility. Among 184 charts reviewed, 14 (7.6%) did not meet ASCCP guidelines for results management. Conclusion: Baseline clinical data indicate significant room for improvement to reduce cervical cancer morbidity and mortality through more effective screening and management of abnormal test results. By employing a learning health system approach, this pre-implementation work has begun to shed light on the resources and processes necessary to support optimal cervical cancer screening management in VISN 23.

Research Topic: Women's Health

27. Genetic Influences on Verbal Memory Efficiency Following a Mild Traumatic Brain Injury

Grund, Peter [1]; Disner, Seth [2]; Sponheim, Scott [2]; Luciana, Monica [1]

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

Abstract: Mild traumatic brain injuries (mTBIs) are common in the U.S. veteran population, and post-concussive symptoms can impact verbal memory performance. While many veterans benefit from cognitive rehabilitation following mTBI, there are others for whom treatment does not result in significant recovery. Identifying genetic biomarkers that influence biological processes underpinning verbal memory may provide additional explanations for discrepancies in mTBI recovery. Deleterious genetic variants associated with the APOE gene, the BDNF gene, and the ANKK1 gene were studied within a veteran population to understand their impact on verbal memory after a mTBI. These three risk alleles have been linked to memory-related deficits and may interact with neuronal repair processes that follow a mTBI. A sample of 257 participants (95% male, mean age =33.2 years (SD =8.3, 22-62), mean months since last TBI =65.7 (SD =30.4) participated in one of two previous studies conducted at the Minneapolis VA. Participants were genotyped and administered neurocognitive measures, including the California Verbal Learning Test-II (CVLT-II), which measures verbal learning and memory capacity. Four memory processes were identified based on a prior factor analysis: Attention Span, Learning Efficiency, Delayed Recall, and Inaccurate Recall. It was hypothesized that the presence of an APOE, BDNF, or ANKK1 risk allele would contribute to poorer performance on the CVLT-II following a mTBI. Our analyses found that the presence of at least one APOE risk allele (E4) was associated with the Delayed Recall CVLT-II factor, and that mTBI history predicted overall CVLT-II performance. mTBI history and APOE risk allele status did not interact in their prediction of memory function. No evidence supported the claim that BDNF or ANKK1 risk allele contributes to verbal memory deficits following a remote mTBI in veterans. These findings do not support the idea that risk alleles in these candidate genes create vulnerability for memory deficits after a mTBI, despite APOE-E4 and mTBI history separately predicting verbal memory deficiencies.

Research Topic: Traumatic Brain Injury (TBI)

28. **Minneapolis Adaptive Design & Engineering (MADE) Program's Licensed Technologies for Veterans**

Hansen, Andrew [1]

1.   Minneapolis VA Health Care System

Abstract: The Minneapolis Adaptive Design & Engineering (MADE) Program was founded in 2010 and has worked to develop and license five products to industry thus far. This presentation will provide a brief overview of the MADE Program team and then show the five products that have been developed and licensed for Veterans. The following technologies will be presented: - Mobile Manual Standing Wheelchair - This system allows Veterans to be mobile while standing in a manual wheelchair, which we believe will increase utility, standing time, and improve health benefits of standing. The MMSW has been licensed to LEVO. - Multi-Purpose Arm Cycle Ergometer (M-PACE) - This system brings exercise to any Veteran including those with spinal cord injuries on sitting restrictions after surgery. MADE developed and tested this system with Veterans and has licensed the technology to Action Manufacturing. - Slope Adaptive Foot (SAF) - The SAF prosthesis automatically adapts to different terrain on every step of walking, allowing Veterans with amputations to more easily and safely navigate uneven terrain. The SAF has been licensed to Fillauer. - Habit Camera - The habit camera allows Veterans at high risk of developing skin pressure injuries to perform improved skin screening, including connections of pictures with health care providers. The Habit Camera has been licensed to Paratroop, LLC. - UNYQ Foot - MADE developed a prosthesis system including multiple modular feet that connect to a single ankle unit. This system will improve footwear options for Veterans with lower-limb amputations, potentially improving body image and participation. This system has been licensed to UNYQ.

Research Topic: Rehabilitative Medicine
Funding agencies: VA RRD
Grant support: VA RRD Merit and SPiRE awards; VA Technology Transfer Program BRAVE funding

29. **Motor performance relationships following lumbar drain in a sample of Veteran patients diagnosed with normal pressure hydrocephalus.**

Hansen, Lucas [1]; Marggraf, Matthew [1]; Thuras, Paul [1]; Doane, Bridget [1]; Lamberty, Greg [1]; McGovern, Robert [1]

1.   Minneapolis VA Health Care System

Abstract: Normal pressure hydrocephalus (NPH) is a disorder of cerebrospinal fluid (CSF) accumulation that causes motor problems in individuals due to excess CSF in the ventricular system, with subsequent compression of the brain. Diagnosis is somewhat imprecise and often relies on clinician judgment. In cases where NPH is suspected, an initial lumbar drain (LD) trial can be completed to assess whether more permanent CSF diversion (via ventriculoperitoneal shunt; VPS) would be beneficial. As VPS placement has the potential to improve quality of life by reducing gait, balance, and in some cases, cognitive impairment (Stolze et al., 2000; Peterson et al., 2016), understanding the relationships between these constructs is important in enhancing clinical decision making. We examined neuropsychological functioning in a group of 21 Veterans with suspected NPH, pre- and post-LD as part of an observational study. Patients were administered a battery of sensitive neuropsychological measures before and after the LD trial. Significant improvements ($p<0.05$) were observed post-LD for bilateral finger tapping speed, stride length, and stride velocity. Initial analyses of the relationships between these variables did not show that the change in dominant (DH) and non-dominant hand (NDH) finger tapping speed correlated with either gait variables post-drain (ps >0.05 for both DH and NDH). Similarly, change in finger tapping performance following LD did not predict change in these gait variables. Thus, while significant motor improvements were observed pre- to post-LD, initial analyses suggest that upper extremity improvements appear to be independent from lower extremity improvements. It is possible that this lack of relationship may be due to the size and characteristics of the current sample. Continued data collection will provide further clarity regarding these relationships. Acknowledging these limitations, preliminary null findings such as these are important when evaluating predictors for post-LD improvement and should be considered in future models.

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

30. Estimating Medication Adherence for Early Identification of Unrecognized Cognitive Impairment in Older Veterans

Harder, Emily [1]; Buteyn, Julia [1]; Westanmo, Anders [1]; Ni Vardeny, Orly [1]; Gravely, Amy [1]; Atwood, Melissa [1]; Fink, Howard [1]

1. Minneapolis VA Health Care System

Abstract: Background: Most dementia is neurodegenerative, with worsening cognitive impairment leading to functional impairment. Although difficulties with medication management are common in patients with clinically recognized dementia, the purpose of this study is to determine if differences in medication adherence in Veterans without documented dementia or cognitive impairment (DCI) can identify those who later will be clinically recognized with DCI. Methods: This retrospective cohort analysis of national Veterans Affairs (VA) data included Veterans aged >65 years; without a baseline DCI diagnosis or prescription for DCI medications; >1 annual VA primary care visit; and receiving an ongoing VA prescription for any of the 4 most commonly dispensed medications during a 3-year adherence assessment period–lisinopril, metoprolol, omeprazole, or simvastatin. Adherence was estimated separately for each medication using proportion of days covered (PDC) or medication possession ratio (MPR), with PDC (or MPR) >0.8 classified as the high adherence category. Participants were followed until the date of incident DCI diagnosis during 10-year follow-up. For each of the above 4 medications, we calculated percent of individuals in adherence categories with incident DCI, then performed Cox proportional hazards survival analysis (HR and 95% confidence intervals) comparing time to first DCI diagnosis. Results: There was a higher percentage of patients later diagnosed with DCI in the low adherence category during 10-year follow-up in all medication groups. Low adherence in each medication category was associated with roughly a 20% increased risk of DCI compared to those in the high adherence group. This magnitude of risk remained consistent with both unadjusted and adjusted analyses. Conclusions: Among Veterans without clinically recognized DCI, lower baseline medication adherence was associated with an increased risk for future clinically recognized DCI. In health systems, automatically generated measures of medication adherence may help identify older adults at risk of DCI who may benefit from cognitive evaluation.

Research Topic: Alzheimer's Disease
Funding agencies: N/A
Grant support: N/A

31. Patterns of Referral for Cognitive Impairment to the GRECC Memory Clinic 2004 to 2019

Hemmy, Laura [1]; Garrett, Sarah [1]; Starks, Jamie [1]; Yuan, Shauna [1]; Fink, Howard [1]; McCarten, J. Riley [1]

1. Minneapolis VA Health Care System

Abstract: Early identification of progressive cognitive decline in older adults is essential for supporting patient agency, accessing services to support transitions and improve quality of life, providing high quality care oriented around cognition, and avoiding at-home crises and presentation for emergency services. However, most older adults still present to medical providers relatively late -- not only after the onset of cognitive changes, but often after substantial functional decline. We evaluated the mean brief cognitive test score for patients presenting to the Geriatric Research, Education, and Clinical Center (GRECC) Memory Clinic, by year from 2004 to 2019, to evaluate whether education efforts to advocate for early identification aimed at patients, providers, and the general public, are resulting in less impaired patients at first referral. The standard brief cognitive test used at GRECC intake was the Mini-Mental State Exam (MMSE) from 2004 to mid 2013, and the Montreal Cognitive Assessment (MoCA) from mid 2013 to 2019. Data analysis of cognitive test scores was capped at 2019 in order to avoid changes in referral and assessment practices after the onset of COVID related precautions in early 2020. The mean MMSE score at intake began at 22.3 in 2004 and ended at 22.1 in 2013 with relatively little variation in between. Mean MoCA scores also did not improve over time and even declined from 19.7 in 2013 to 16.7 in 2019. Not only are patients not being referred earlier (at a less impaired cognitive state) over time, but there has been some decline in recent years. These data cannot identify whether this observation is the result of provider reluctance to refer, patient reluctance to present, or other system factors.

Research Topic: Alzheimer's Disease
Funding agencies: N/A
Grant support: N/A

32. Brief Self-Compassion Training for Burnout among Medical Residents

Himmerich, Sara [1]; Bronars, Carrie [1]; Urosevic, Snezana [1]; Possis, Elizabeth [1]

1. Minneapolis VA Health Care System

Abstract: Burnout is a significant issue among medical providers and is associated with decreased job satisfaction, physical ailments, medical errors, and poor mental health. Moreover, burnout is more prevalent among providers younger than 40, with medical training representing a peak time of distress (Dyrbye & Shanafelt, 2016). In past studies, resiliency factors have demonstrated an inverse relationship with burnout in a sample of medical providers (Buck et al., 2019). Additionally, greater self-compassion has been associated with lower levels of burnout among medical providers and may be conceptualized as a ""resilience type resource"" that is important for managing stress (Hashem & Zeinoun, 2020). A large body of research in other populations demonstrates that brief interventions can enhance self-compassion, and that self-compassion is a skill that can be improved through targeted practice. The current project is the first to examine the acceptability and impact of a brief program promoting brief self-compassion training on resilience and burnout among medical residents. Prior to the training sessions, residents completed an initial questionnaire packet that assessed demographic information (i.e., age, year of training) and baseline levels of burnout, self-compassion, and overall resilience. Next, the group training was conducted in three sessions over three weeks. The first session included psychoeducation about self-compassion and individual written exercises. The next two sessions each included a brief self-compassion exercise. The final session also assessed satisfaction with the training and post-training levels of burnout, self-compassion, and overall resilience. Data collection and training sessions were all conducted virtually and data collection was completed in March 2022. Planned analyses will examine the present self-compassion skills training's impact on reduction in burnout and increase in overall resiliency during internal medicine residency training. It will also provide information on changes in self-compassion that occur by participating in a brief intervention. Further, the project's results could inform recommendations for feasibility of a brief self-compassion intervention delivered in a medical training setting.

33. We don't have to talk about it: The role of symptom accommodation in trauma-focused treatment engagement and response.

Howard, Kristen [1]; Spoont, Michele [1]; Polusny, Melissa [1]; Eftekhari, Afsoon [2-3]; Rosen, Craig [2-4]; Meis, Laura [1]

1. Minneapolis VA Health Care System
2. National Center for PTSD
3. VA Palo Alto Health Care System
4. Stanford University

Abstract: Among veterans, rates of PTSD following treatment remain high (Steenkamp et al., 2015) while treatment engagement remains a significant challenge (Hale et al., 2019; Maguen et al., 2019). Symptom accommodation by loved ones may be particularly relevant to treatment engagement yet has remained relatively understudied in the context of PTSD (Reuman & Thompson-Hollands, 2020). We examined the role of symptom accommodation by support persons (SP) in veterans' PTSD treatment response, including the mediating role of treatment engagement and the moderating influence of relationship distress. Veterans engaging in Prolonged Exposure or Cognitive Processing Therapy and a loved one (n=279 dyads) were sampled at two time points, approximately four months apart. The highest session attended and homework completion were obtained from hospital records. We used mediation and moderation regression analyses to examine the effect of accommodation on treatment engagement and response (controlling for SP relationship type, number of sessions completed prior to first survey, and time 1 PTSD scores). SP accommodation was not significantly related to either treatment engagement variable, nor was it related to treatment response. However, there was a significant interaction between accommodation and relationship distress in relation to treatment response, such that accommodation significantly predicted higher PTSD scores after treatment among those with lower relative relationship distress. Finally, we examined treatment engagement as mediators of treatment response. We found that homework completion, but not highest session, significantly mediated the association between SP accommodation on PTSD outcomes. In the same model, the direct effect of SP accommodation was again moderated by relationship distress, with accommodation predicting greater PTSD scores among only those with below average relationship distress. This suggests two pathways through which accommodation may influence PTSD outcomes both directly and indirectly. Attending to the accommodating behaviors of veterans' supportive partners, particularly in the context of lower homework compliance, may be an important way to boost the effects of PTSD treatments.

34. MEG Neural Signature of Sexual Trauma in Women Veterans with PTSD

James, Lisa [1]; Leuthold, Arthur [1]; Georgopoulos, Apostolos [1]

1.   Minneapolis VA Health Care System

Abstract: Previous research has documented the utility of synchronous neural interactions (SNI) in classifying women veterans with and without posttraumatic stress disorder (PTSD) and other trauma-related outcomes based on functional connectivity using magnetoencephalography (MEG). Here we extend that line of research to evaluate trauma-specific PTSD neural signatures with MEG in women veterans. Participants completed diagnostic interviews and underwent a task-free MEG scan from which SNI was computed. Twenty-two women veterans were diagnosed with PTSD due to sexual trauma and seven with PTSD due to non-sexual trauma. Linear discriminant analysis was used to classify the brain patterns of women with PTSD due to sexual trauma and non-sexual trauma and their respective brain patterns were compared. Using SNI, the brains of participants were classified as sexual trauma or non-sexual trauma with 100% accuracy. Patterns of SNI were highly overlapping in both groups, although sexual trauma was characterized by more intense involvement of bilateral anterior temporal regions and a central sulcus/midline region compared to the non-sexual trauma group. These findings bolster evidence supporting the utility of task-free SNI and suggest that neural signatures of PTSD are trauma-specific.

Research Topic: Posttraumatic Stress Disorder (PTSD)
Funding agencies: VA CSRD
Grant support: I01CX001045

35. Engaging Veterans as partners in research

Jensen, Agnes [1]; Amundsen, Erin [1]; Branson, Mariah [1]; Campbell, Emily [1]; Mahaffey, Mallory [1]; Mass, Andy [1]; Valentin, Noel [1]; Sides, Tracy [1]; Siver, Malloree [1]; Ullman, Kristen [1]; Meis, Laura [1]; Veteran Engagement Panel partners

1.   Minneapolis VA Health Care System

Abstract: Minneapolis VA's Center for Care Delivery and Outcomes Research (CCDOR) is emerging as a national leader in engaging Veterans in research. Nearly 70 Veterans from the Minneapolis area and across the country collaborate with CCDOR researchers and beyond to provide patient-centered feedback throughout the research process, from grant development through dissemination. Veteran partners are members of seven Veteran Engagement Panels (VEPs); each VEP focuses on a research area (i.e. chronic pain, women's health, trauma recovery/PTSD) or supports a specific study or initiative. A VEP typically has 7-12 members, reflecting the diversity of the Veteran population in terms of gender, race/ethnicity, service era and life experience. VEP members attend virtual meetings via Web-Ex/Zoom and are compensated. Some in-person meetings will resume in 2022. The Veteran Engagement Workgroup (ViEW) includes CCDOR staff (three who are Veterans themselves) who plan and facilitate meetings between research teams and VEPs. At these meetings, VEP members review recruitment materials, discuss how to attract and retain Veterans into research studies, and provide input on disseminating findings to Veteran and caregiver communities. VEP members have given feedback on a variety of research types, including clinical trials, survey studies, and secondary data analyses. Researchers work with the Veterans not as subjects, but as colleagues. ViEW staff have facilitated dozens of VEP meetings in the past four years. For successful Veteran engagement panel meetings, the ViEW recommends to 1) avoid unstructured large group conversations; 2) limit each meeting to a few clear discussions; 3) ensure all members receive adequate 'floor time' to share; 4) use first names to break down hierarchal structure; 4) provide smaller breakouts for deeper discussions when appropriate; and 5) cultivate a welcoming, non-judgmental environment for Veterans to feel safe and their input valued. After each meeting, both researchers and VEPs are invited to evaluate their experiences. Researchers are asked to share how they incorporated VEP advice into their research project. Long term, ViEW follows up with researchers to track impacts of VEP input such as successful grant funding, improved recruitment, or retention success. VEP members have co-authored publications with researchers and co-presented at conferences. CCDOR's ViEW shares best engagement practices with other researchers and is available for consultation.

Research Topic: Health Services
Funding agencies: VA HSRD; DOD
Grant support: PCORI

36. Effects of Nurse Staffing on Nursing Home Outcomes: A Systematic Review

Jutkowitz, Eric [1-2]; Landsteiner, Adrienne [3]; Ratner, Edward [3-4]; Shippee, Tetyana [4]; Ullman, Kristen [3]; Linskens, Eric [3]; Madrigal, Carolyn [1]; Wilt, Timothy [3-4]; Duan-Porter, Wei [3-4]

1. Providence VA Medical Center
2. Brown University
3. Minneapolis VA Health Care System
4. University of Minnesota

Abstract: Background: More than 1.3 million US adults reside in over 15,000 US nursing homes. Nursing homes are complex environments serving a variety of resident needs, including rehabilitative post-acute, end-of-life, or custodial long-term care. It remains unclear how direct care nurse staffing levels and skill mix impact outcomes, such as rates of pressures ulcers, infections and moderate-severe pain among residents. To guide VA partners on potential recommendations for VA nursing homes and State Veterans Homes, we conducted a systematic review on the effects of nurse staffing on resident outcomes. Methods: We searched MEDLINE, Embase, CINAHL, and the Cochrane Database for English-language articles published from January 2000 to May 2021. We also hand-searched bibliographies of identified relevant systematic reviews, and grey literature. Search results were independently reviewed by 2 investigators for eligibility. For eligible studies, 2 reviewers independently assessed quality and data abstraction was undertaken by one reviewer with over-reading by a second reviewer. Abstracted data included: study design (including data sources, detailed analytic methods and definitions of nurse staffing and/or skill mix); setting and population characteristics; and results on processes of care or resident outcomes. We rated overall certainty of evidence using GRADE. Results: Of 9,152 unique titles and abstracts screened, 378 articles underwent full-text review and 44 studies were eligible. Fifteen articles addressed pressure ulcers, 12 examined infections in nursing homes, and 7 looked at moderate-severe pain among residents; additional articles looked at a variety of other outcomes. All studies used observational data and most were cross-sectional. Overall, registered nurse (RN) staffing was associated with fewer pressure ulcers (moderate confidence), fewer infections (low confidence), and lower rates of moderate-severe pain (low confidence). Results for these outcomes associated with other nursing staff, total staffing, and skill mix were more mixed and rated as low or very low confidence. Conclusions: Higher RN staffing may be associated with better resident outcomes, but the magnitude of effects were generally very small. Randomized study designs may be required to definitively understand the causal effects of nurse staffing on resident outcomes.

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37. Ventriculomegaly in Normal Pressure Hydrocephalus (NPH) versus Alzheimer's Dementia (AD)

Kadaba Sridhar, Sharada [1]; Kuang, Rui [1]; Samadani, Uzma [2]

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

Abstract: Normal Pressure Hydrocephalus (NPH) is currently thought to be the only type of dementia that is reversible through diversion of cerebrospinal fluid (CSF) using a shunt. Less than 20% of patients get a correct diagnosis due to overlapping clinical symptoms with Alzheimer's Disease (AD) and Parkinson's Disease (PD). Invasive tests for lumbar drainage and intracranial pressure evaluation remain as standard diagnostic tools, along with clinical and radiographic image evaluation. Non-contrast computed tomography (NCCT) offers rich insight into the morphology of ventricles. Apparent dilation of ventricles due to atrophy in AD should not be confused with enlargement due to excessive CSF in NPH. Algorithmically extracting features indicative of ventriculomegaly in an automated way (with minimal manual input) can help to provide accurate, non-invasive, affordable, and timely diagnosis. We developed computational pipelines to extract measures that can identify enlargement at different points of the lateral and third ventricles with minimal manual input required for standardization of the NCCT scans. These measures are then used to classify between non-shunted patients with idiopathic NPH and those with AD, as identified on the VA Informatics and Computing Infrastructure (VINCI) database. Patient demographic variables such as age and gender, among others are used in classification to establish a baseline for performance. Using different machine learning models for supervised classification, we report the accuracy, sensitivity, specificity, and AUC measures for objective classification using the computationally derived NCCT features indicative of ventriculomegaly versus atrophy. This work has strong potential to be incorporated into routine clinical practice.

38. Exploration Patterns of Dropout in Phased and Concurrent Treatment for Posttraumatic Stress Disorder and Substance Use Disorder

Kaplan, Adam [1]; Alpert, Elizabeth [2]; Nelson, David [1]; Kehle-Forbes, Shannon [1]

1. Minneapolis VA Health Care System
2. VA Boston Health Care System

Abstract: Background: Veteran attrition remains a pervasive problem in trauma-focused therapies (TFTs) for post-traumatic stress disorder (PTSD) and for Veterans with both PTSD and substance/alcohol use disorder (SUD/AUD) dropout rates are even higher. It is well established that attending an appropriate number of sessions (e.g., 8 or 12) strengthen Veterans in terms of reducing PTSD symptoms and, in some studies, better long-term substance use outcomes. To benefit from TFTs, it is essential to understand and reduce the impact of factors leading to dropout. Post-hoc studies have used baseline measures (e.g., age and sex) to explain dropout but they do not capture the entire course of it. It is a temporal process presumed to relate with the symptomology, i.e., the within-treatment measures. Measures such as PCL (measuring PTSD symptomology), SIP-R (measuring consequences of use), and percent-use of substances in the last month (TLFB), are candidates to better explain variability in TFT dropout. But, current statistical approaches to pinpoint these relationships are lacking. The common way to model dropout is a survival model, i.e., each session has a probability of dropout. When using within-treatment measures as a predictor of dropout risk it is custom to use them as time-varying predictors. This approach precludes therapists from saying at which session does PCL change impact dropout. Moreover, it does not pinpoint for whom this symptom change escalates dropout. Therefore, we introduce an approach to appropriately model within-treatment measures and indicate Veteran subgroups, based on symptom changes, with different patterns of dropout. Methods: We first cluster Veterans into groups sharing similar symptom trajectories of substance use and PTSD using Bayesian Semi-Parametric Trajectory Analysis. We then use these clusters as predictors of dropout at each subsequent session, instead of modeling an overall drop-out risk per cluster (i.e., the standard time-varying set-up). Our data application uses 183 Veterans with PTSD-SUD randomized to two different interventions in the STRIVE clinical trial. We also compare our approach to simpler survival models. Results: Partitioning Veterans into symptom-change clusters greatly improved model fit but added larger complexity. Our approach supports previous anecdotal evidence that Veterans already with low and decreasing PTSD symptoms dropout early whereas the Veterans with consistently high TLFB associated with early dropout.

39. Euglycemic DKA in the Setting of SGLT2 Inhibitor Therapy Demands Cardiologists' Awareness and Revision of Standardized Treatment Protocols

Lehenbauer, Katy [1-2]; Tsangaris, Adamantios [1-2]; Bart, Bradley [1]

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

Abstract: Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a popular new class of medications for patients with type 2 diabetes mellitus (T2DM) due to promising morbidity and mortality benefit in those with cardiovascular disease or with increased risk. However, a potential side effect is euglycemic diabetic ketoacidosis (EDKA), which can be fatal without early recognition and treatment. Case: A 52 year-old male with T2DM on an SGLT2 inhibitor, empagliflozin, presented to the hospital with two days of chest pain, polyuria, and nausea with poor oral intake. ECG showed ST elevation in the lateral leads consistent with acute lateral myocardial infarction and met clinical criteria for EDKA, with labs showing an anion gap of 23, venous pH of 7.07, ketonemia, and blood glucose (BG) of 195 mg/dL. The patient underwent emergent percutaneous coronary intervention (PCI) and received a drug-eluting stent in an obtuse marginal artery. Following PCI, treatment of EDKA was delayed because the hospital protocol required a BG >350 mg/dL to initiate an insulin drip. After manually entering orders for fluid, insulin, and dextrose, the anion gap closed, the acidosis resolved, and the patient was ultimately discharged home. Decision-making: Despite relative euglycemia, the patient's critical condition was immediately recognized as EDKA. Unfortunately, treatment was delayed considerably due to PCI and the hospital's standardized DKA protocol limitation of not taking into consideration patients such as this who present with profound ketoacidosis yet remain euglycemic. Deviation from an otherwise familiar protocol created a logistical challenge for the treatment team and thus required an extensive amount of clarification and manual order entry prior to execution. Conclusion: EDKA in the setting of infarction and SGLT2 inhibitors is becoming an increasingly common presentation, so it is essential for treating physicians to be aware of this entity and that hospital protocols are updated to facilitate early treatment. There should be a low threshold to check blood pH and ketone levels regardless of BG level in undifferentiated patients presenting to the emergency department who are taking an SGLT2 inhibitor.

40. **Effect of dopamine-replacement therapy on the gambling impulsivity of Parkinson's patients**

Lewis, Scott [1]; Hemmy, Laura S. [1]; Pellizzer, Giuseppe [1]

1. Minneapolis VA Health Care System

Abstract: Dopamine-replacement (DR) therapy has been associated with an increase in impulsive behavior in Parkinson's disease (PD) patients. Impulsivity has been linked to increased fall risk in PD patients, and an altered quality of life. When impulsivity reaches the levels of impulse control disorders, it can lead to financial ruin, marital distress, and more generally negatively affect patients and their family's quality of life and emotional well-being. For these reasons, more research is critically needed to better understand the DR-induced impulsivity in PD, and to develop more effective care. The goal of our project is to compare the outcome of behavioral tests (Iowa gambling task and go/no-go task) and functional brain measures in PD patients while they are on and off DR. The Iowa gambling task tests decision-making abilities in a simulated card game, whereas the go/no-go task tests the ability to abort a preponderant motor response. Here we present preliminary results on the change in performance in the behavioral tasks of N=23 PD patients while in on versus off DR medications. Using a cluster analysis, we found that 65% (15/23) of PD patients had significantly more impulsive behavior in the Iowa gambling task while in on versus off DR medication. They made significantly more unfavorable choices and lost significantly more play money in the on DR medication condition compared to the off medication condition. In contrast, we found no significant effect of the medication condition on the go/no-go task. The results show that DR medication significantly increased impulsive behavior of PD patients in a simulated gambling task. In the near future we will analyze magnetoencephalography data recorded while the patients performed the tasks to extract functional brain activity biomarkers that reflect the susceptibility to DR-induced impulsivity. We expect that the outcome will provide a better understanding of the brain mechanisms associated with impulsivity and how those are affected by DR medication in PD.

41. **Longitudinal Predictors of Intimate Partner Violence following Military Deployment: A comparison between Soldier-only Versus Bidirectional use of Violence in Romantic Dyads**

Lipinski, Alexandra [1]; Polusny, Melissa [1]

1. Minneapolis VA Health Care System

Abstract: Intimate partner violence (IPV) is a highly prevalent and serious public health problem in the United States. Relative to civilians, Veterans, particularly those with PTSD, are more likely to both experience and engage in IPV. Although IPV is typically characterized as being enacted by one partner in a romantic relationship (i.e., unidirectional IPV), a growing body of literature demonstrates that bidirectional IPV (i.e., both partners' use of violence) is the most common pattern of violence within intimate relationships. Little is known about factors contributing to bidirectional IPV. The present study longitudinally examined soldier mental health and dyadic IPV as predictors of uni- and bidirectional IPV following deployment (n=490 dyads). Methods: Data from the Readiness and Resilience in National Guard Soldiers (RINGS-2) project were examined for each partner. Data were collected 2-5 months prior to deployment and within one year following soldier's return. Results: Hierarchical logistic regression evaluated predictors of uni- and bidirectional physical, sexual, and psychological IPV. Across all models, soldier age and prior OEF/OIF deployment status were examined in the first block of the equation. The second block included pre-deployment soldier and partner use of IPV and soldier PTSD symptoms (PTSS). The third block included soldier post-deployment PTSS and alcohol use. After adjusting for multiple comparisons, the full multivariate models predicting post-deployment soldier-only IPV were statistically significant for physical IPV only ($p<0.001$). Partner use of pre-deployment physical IPV was associated with soldier-only post-deployment physical IPV ($p<0.001$). For bidirectional IPV, Soldier post-deployment PTSS predicted bidirectional physical IPV ($p<0.001$). Prior OEF/OIF deployment ($p=0.003$), partner use of pre-deployment psychological IPV ($p<0.001$), and soldier post-deployment PTSS ($p=0.006$) each predicted the post-deployment bidirectional psychological IPV. No significant predictors emerged for sexual IPV. Discussion: This study found nuanced associations between mental health variables and uni-vs. bidirectional IPV following a military deployment. Full results and implications will be discussed.

42. **Acceptability of Adaptive Disclosure-Enhanced and Present Centered Therapy among Veterans with PTSD and Moral Injury**

Luskey, Valerie [1]; Litz, Brett [2]; Harris, Irene [1]; Usset, Timothy [1]; Evans-Lindquist, Mary [1]; Moran, Amy [1]; Borst, Jacob [1]; Nienow, Tasha [1]

1. Minneapolis VA Health Care System
2. VA Boston Health Care System

Abstract: Veterans are not always able to tolerate psychotherapy interventions for PTSD, and the rate of premature drop out has been reported to be between 25-40%. More recently, psychotherapy interventions have been developed for individuals who experienced PTSD and moral injury. This study aimed to examine the tolerability of a novel approach to the treatment of PTSD and moral injury called Adaptive Disclosure-Enhanced (AD-E). A multi-site clinical trial comparing the efficacy of AD-E to Present-Centered Therapy (PCT), a PTSD intervention that does not target moral injury, was recently completed. Data from 68 Veterans enrolled in the study at the Minneapolis site was examined to compare rates of completion between AD-E and PCT. Exploratory analyses were conducted to examine whether differences were observed between completers and dropouts at baseline on demographics, psychosocial functioning, and symptom severity. All participants were administered the: Sheehan Disability Scale (SDS), Brief Inventory of Psychosocial Functioning (BIPF), Patient Health Questionnaire-9 (PHQ-9), Moral Injury Event Scale (MIES), and PTSD Checklist for DSM-5 (PCL-5). Participants assigned to AD-E and PCT did not differ at baseline on demographics, social functioning, or symptom severity. Only a trend was noted on the MIES for perceived transgressions, with participants in PCT reporting more than AD-E participants, p=0.05. Both AD-E and PCT had comparable rates of premature dropout, 38.2% and 35.30%, respectively. Comparison of completers versus dropouts revealed that women were more likely to complete treatment, p=0.03. When correlates of completion were examined within each condition, additional relationships emerged. AD-E completers had more deployments than AD-E dropouts, p=0.02. In contrast, PCT completers reported greater psychosocial distress (p=0.02), disability (p=0.03), and symptom severity (p=0.05) at baseline then PCT dropouts. Results suggests that different factors motivated participants to complete treatment in each condition. AD-E, with its focus on the morally injurious event and sensitivity to military culture, appears to have appealed more to Veterans with multiple deployments. In contrast, among Veterans who reported greater awareness of difficulty coping with current interpersonal stressors and symptoms, PCT, with its focus on coping with current concerns, appears to have motivated treatment completion. Implications of these findings will be discussed.

Research Topic: Posttraumatic Stress Disorder (PTSD)
Funding agencies: VA RRD
Grant support: I01RX002135

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43. **Changes in neuropsychological test performance in Veterans with presumed normal pressure hydrocephalus following extended lumbar drain trial.**

Marggraf, Matthew [1]; Hansen, Lucas [1]; Doane, Bridget [1]; McGovern III, Roberty [1]; Lamberty, Gregory [1]

1. Minneapolis VA Health Care System

Abstract: Normal pressure hydrocephalus (NPH) is a condition of excess cerebrospinal fluid (CSF) accumulation resulting in gait disturbance, urinary incontinence, and cognitive impairment. Although temporary CSF diversion techniques (e.g., lumbar drain; LD) are effective in improving gait, inconsistent findings have been noted for neurocognitive functioning. Findings likely reflect methodological differences (battery length, follow-up duration, practice effects), several of which are addressed in this study. We examined neuropsychological functioning in a group of Veterans with suspected NPH (n=24), pre- and post-lumbar drain. Patients were administered a battery of sensitive neuropsychological measures before and after the LD trial, utilizing alternate forms to mitigate practice effects. Significant improvement (p<0.05) was observed post-LD for phonemic fluency and bilateral finger-tapping speed. Trend-level improvement (p=0.063) was observed on an executive set-shifting measure. Measures of attention, working memory, processing speed, or verbal learning/memory revealed no differences. Temporary CSF diversion appears to have a more pronounced effect on speeded operations (e.g., verbal fluency, finger-tapping) compared to other cognitive domains. Results suggest subtle cognitive changes may be identifiable when using the LD procedure to simulate more permanent CSF diversion (i.e., ventriculoperitoneal shunt).

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

44. Experiential Avoidance Predicts Brain Responses to Stressful Task Demands

Marquardt, Craig [1]; Teich, Collin [2]; Stevens, Kara [2]; Sponheim, Scott [1]; Polusny, Melissa [1]

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

Abstract: Background: Experiential avoidance is a behavioral unwillingness to remain in contact with unpleasant experiences (e.g., thoughts, feelings), and a transdiagnostic psychological process associated with the development and maintenance of psychopathology. Although avoidance produces short-term relief from discomfort, it prevents long-term learning about distress tolerance. Methods: We administered a Go/No-Go task to recruits in a National Guard (n=114). Participants responded to 'Go' stimuli and withheld responses to 'No-Go' stimuli. The second task block was challenging due to adaptive response windows, which served as a stressor analog. The third task block functioned as a recovery period to measure experiential avoidance vs. psychological flexibility. We assessed event-related potentials (ERPs) for N2 (175-275 ms) and P3 (275-450 ms) at the frontal FCz electrode. Participants also completed the Multidimensional Experiential Avoidance Questionnaire (MEAQ; G·mez et al., 2011). Results: N2 responses were potentiated during No-Go relative to Go trials, but only during the third block (i.e., post-stressor recovery period). Furthermore, P3 responses were potentiated during the No-Go relative to Go trials, but the differences were smallest during the third block. Associations with experiential avoidance were specific to P3. Greater MEAQ-Distress Aversion was associated with a lack of P3 decreases during this third block (b=0.031, 95% CI [0.010, 0.052], β=0.199). Conclusions: The results point to non-acceptance of discomfort and negative attitudes towards distress as relevant for adaptation and attentional control following exposure to stressors. Distress intolerance may be a useful longitudinal predictor of impaired resilience among new soldiers experiencing military-related challenges.

45. Veteran Feedback and Testing of a Lightweight Ergonomic Wheelchair

Mavanji, Vibha [1]; Comstock, Brogan [1]; Sauerbrey, Matt [1]; McCracken, Patricia [1]; Froechtenigt, Abigail [1]; Wacek, Amber [1]; Hansen, Andrew [1]; Goldish, Gary [1]; Looft, John [1]

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

Abstract: The purpose of our study was to collect quantitative kinematic data and gain Veteran feedback describing the usability and functionality of a novel ergonomic wheelchair (EWC) design. Prior research has demonstrated suboptimal wheelchair push rim placement can lead to pain and functional decline in wheelchair users. Understanding how wheelchair design affects the user is imperative for preserving manual wheelchair use and maintaining mobility with the goal of preventing the decline of quality of life. Our first hypothesis was the novel EWC would produce a decrease in peak muscle activation as a percent of maximal voluntary contraction of the anterior deltoid and pectoralis major muscles during the push phase. Our second hypothesis was the EWC will significantly reduce shoulder abduction, extension, and external rotation during the push phase, allowing for more time in the workable range of motion. Ten Veterans completed the data collection protocol comparing propulsion in the EWC and a standard Tilite wheelchair. Kinematic analysis, surface electromyography (EMG), wheelchair outcome measures, and Veteran feedback were collected to analyze the function and usability of the wheelchair. Wheelchair propulsion was measured using a 22 camera Qualisys motion capture system and muscle activity was measured using a 16 channel Delsys Trigno wireless EMG. A modified wheelchair skills test was used to capture functional outcome measures of wheelchair function and an open-ended interview was conducted to capture Veteran feedback. Thematic analyses of Veteran feedback showed six areas of focus related to function, design, and usability. Comments within participants' feedback included ""The ergonomic wheelchair serves a purpose"" but also included statements such as the wheelchair being ""Not as good for everyday use."" Two-way ANOVA testing of the kinematic, spatiotemporal, and EMG data demonstrated very little differences in physical performance between the wheelchairs. However, there were significant findings for shoulder flexion and extension (p=0.0138 at 0% of push cycle and p=0.0095 at 100% of push cycle) and wrist flexion and extension (p=0.0014 at 25% of push cycle) along with distance traveled per stroke (p=0.0303). Veteran feedback in conjunction with the additional qualitative measures substantiate the need for including the population for which the wheelchair is designed in the design and pilot research process.

46. Orexin A enhances neuronal synchronization in adult rat hypothalamic culture: A model to study hypothalamic function.

Mavanji, Vijayakumar [1]; Georgopoulos, Apostolos [1]; Kotz, Catherine [1]

1.   Minneapolis VA and University of Minnesota

Abstract: The regulation of sleep/wake behavior and energy homeostasis involves the lateral-hypothalamic (LH) neuropeptide orexin A (OXA). A reduction in orexin function results in sleep disorders and obesity, whereas higher orexin signaling and sensitivity promotes obesity resistance. Similarly, dysregulation of hypothalamic neural network is associated with onset of age-related diseases, including obesity. Despite the increase in obesity with aging, and that adult populations are the subjects in the majority of obesity studies, conventional models for neuronal networks utilize embryonic neural cultures rather than adult neurons. Synchronous neural activity is a feature of normal brain function, which indicates correlated changes in neuronal activity between neurons, and determines the nature of final output from a given neural structure. Neural synchrony is altered by behavioral perturbations, in embryonic neurons obtained from obesity-resistant rats, and following application of OXA onto embryonic hypothalamic cultures. Synchronous activity in adult hypothalamic neurons remain largely undescribed. We established an adult rat hypothalamic culture in multi-electrode-array (MEA) dishes and recorded the field potentials. Then we studied the effect of exogenous OXA on network synchronization of these cultures. In addition, we studied the wake promoting effects of OXA in vivo when directly injected into the rostral lateral hypothalamus (rLH) of rats that were implanted with a radiotelemetric transmitter and EEG/EMG electrodes to record vigilance states (Data Sciences International [DSI], St. Paul, MN), and a cannula targeting the rLH. Either OXA (250 pmol) or saline was infused into the rLH (single injection) and sleep/wake states were measured for 2h post-injection. The results show that adult hypothalamic cultures are viable for nearly 3 months in vitro, good quality MEA recordings can be obtained from these cultures, and finally, that cultured adult hypothalamus is responsive to OXA. In addition, LH administration of OXA enhanced wakefulness in rats, indicating that OXA enhances wakefulness for up to 2h post-injection. The results support that adult rat hypothalamic culture could be used as a model to study the neural mechanisms underlying obesity, and that obesity resistance is associated with increased hypothalamus synchronization. Increased wake following rLH OXA suggest the possibility that OXA promotes wake partly by promoting hypothalamic neural synchrony.

Research Topic: Obesity

47. Predeployment Negative Emotionality Amplifies Associations Between Postdeployment Pain and Pain Disability

McDermott, Katherine [1]; Marquardt, Craig [1-2]; Arbisi, Paul [1-2]; Polusny, Melissa [1-2]

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

Abstract: Background/Objectives: Associated features of chronic pain, including perceived disability and substance use, can vary widely even among individuals who report similar levels of pain. The Minnesota Multiphasic Personality Inventory (MMPI) has been shown to provide useful information about psychological factors that could influence pain development and recovery, with previous research demonstrating associations between negative emotionality and low positive emotion with worse outcomes (Block et al., 2017; Vendrig et al., 2000). The present study investigated the interaction between pain symptoms and three competing personality trait dimensions from the Minnesota Multiphasic Personality Inventory (MMPI) PSY-5 scales as moderators of these associations, hypothesizing that there would be stronger associations between pain symptoms and disability for those with higher negative emotionality (NEGE-r) and introversion/low positive emotion (INTR-r), and stronger associations between pain and AUD symptoms for those with elevated disconstraint (DISC-r). Methods: This is a secondary analysis of the Readiness and Resilience in National Guard Soldiers study, in which U.S. National Guard soldiers completed measures of personality and physical and mental health symptoms before and after deployment (n=1291). The MMPI-2-RF was administered at baseline. Follow-up measures included pain intensity, disability, AUD symptoms, and somatic symptoms. Linear regression models with interaction terms were used to compare three competing moderators in the same model. Results: NEGE-r, but not INTR-r or DISC-r, interacted with pain intensity, such that the association between pain intensity and disability was greater for those with higher (β=0.86, p<0.001) than lower (β=0.77, p<0.001) baseline NEGE-r. Similar results were found with somatic symptoms used in place of pain intensity to replicate and extend the initial findings. No interactions predicted AUD symptoms. Conclusion: The presence of negative emotionality may amplify the experience of pain and lead to worse pain disability. It may be important to consider underlying personality factors when evaluating correlates of worse pain disability. The present study was strengthened by the pre-deployment assessment of negative emotionality, suggesting an underlying proneness to stress reactivity, worry, and anger may factor in the experience of pain years later.

Research Topic: Pain

48. Million Veterans Program (MVP): A Partnership with Veterans

Murdoch, Maureen [1-2]; Bender, Tricia [1]; Pahl, Marissa [1]; Dorman, Christopher [1]

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

Abstract: Purpose: The goal of the Million Veteran Program is to improve the health of veterans through better prevention, diagnosis, and prevention of disease. This is facilitated through the investigation of the link between genes, military exposures, lifestyle factors, and health and wellness. Intro: MVP is a national, voluntary research program conducted by the VA and OR&D and one of the VA's initiatives to improve healthcare. The Million Veteran Program collects genetic and health information to help find new ways of prevention, early detection, and treatment of illness. MVP is providing a better understanding of how genes affect health and illness with the goal of improving health care for veterans using genomic analysis of participant samples, computerized patient records, and health surveys. Nationally, over 880,000 veterans have enrolled at 57 VAs with 20,828 at the Minneapolis VACHS as of 4/21/22. Methods: Participation involves: 1. Completing a one-time study visit to cover informed consent and provide a blood sample for genetic testing. 2. Filling out baseline and lifestyle surveys. 3. Permitting authorized MVP staff access to health records on an ongoing basis. 4. Agreeing to future contact. Individual studies approved by the appropriate oversite committees then have access to deidentified MVP data for analysis. The highest priority projects approved to utilize MVP data are focused on issues that are most relevant in our veteran community. These studies will not only provide valuable research results but also help to develop and streamline the data access procedures for future researchers. There are over 500 current studies spanning a variety of topics ranging from mental health, substance dependence, traumatic brain injuries, cardiovascular disease, Alzheimer's disease, nephrology, oncology, rheumatology, immunology, proteomics, sleep disturbances, and Covid-19 among many others.

Research Topic: Genomics
Funding agencies: N/A
Grant support: MVP 000

49. Improving Footwear Options for Veterans With Lower Limb Amputation

Nickel, Eric [1]; Walker, Nicole [1-2]; Yun, Kelly [1]; Hansen, Andrew [1-2]

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

Abstract: For persons with lower limb amputation, maintaining proper alignment of the prosthetic foot relative to the ground is an essential part of successful clinical outcomes and prevention of secondary injuries, such as back pain, joint breakdown, or skin breakdown within the prosthetic socket. The prosthetic alignment factors in the shoes worn during the fitting and alignment process in the clinic. When the lower limb prosthesis user purchases another pair of shoes, they are presented with two options: find shoes with essentially the same exact heel rise (often purchasing multiple pairs to avoid this issue in the future) or return to the prosthetist for a realignment. Women Veterans that use lower limb prostheses often cannot wear their footwear of choice due to this static alignment. Prosthetic feet that allow self-adjustment of the alignment can render void the expert clinical alignment, leading again to the aforementioned secondary injuries, and only provide a limited range of heel rises that can be accommodated (up to 2 inches). Our project is to develop a prosthetic foot-ankle system that supports women Veterans with wearing their footwear of choice throughout the day. To achieve this goal, we have developed a prosthetic ankle unit that interfaces with 3D printed prosthetic feet each custom made to factor in the heel rise of a particular pair of shoes. A quick release system supports rapid swapping of feet as the desired footwear changes throughout the day. Shoe heel heights up to 4 inches can be accommodated. This novel prosthetic ankle-feet system has been licensed to an industry partner and is being refined into a commercial product. Current initiatives are focused on enabling compliance for off-axis rotations (multiaxial function) and improving cosmetic appearance. The 3D printed feet have demonstrated superb strength when tested with our ISO 10328 test machine.

Research Topic: Prosthetics
Funding agencies: VA RRD
Grant support: I01RX002634; BRAVE funding, VA Technology Transfer Program

50. White Matter Integrity Moderates the Association Between Remote Blast-Related Mild TBI and Executive Control

O'Brien, Molly [1]; Disner, Seth [2]; Davenport, Nicholas [2]; Sponheim, Scott [2]

1. Macalester College
2. Minneapolis VA Health Care System

Abstract: Mild traumatic brain injury (mTBI) is a critical research area in recent combat veterans due to increased prevalence of survived blasts. Post-mTBI outcomes are highly heterogenous and defining neurological differences may help in discrimination and prediction of cognitive outcomes. This study investigates if white matter integrity, measured with diffusion tensor imaging (DTI), could influence how remote mTBI history is associated with executive control. The sample included 182 veterans from the Minneapolis VA Medical Center who were administered a clinical/TBI assessment, neuropsychological battery, and DTI scan as part of a larger battery. From previous research, five white matter tracts were identified as having a relationship with blast severity: the cingulum, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and uncinate. Fractional anisotropy (FA) of the a priori selected white matter tracts, PTSD severity, and mTBI severity (separated into blast and impact scores) were used as predictors of Trail-Making Test B (Trails B) performance in a multiple linear regression model. In veterans with history of blast mTBI, the association between blast severity and Trails B was moderated by FA of the right hippocampal cingulum (CGHR), shown by a significant interaction ($p=0.0011$), such that lower FA increased the association between blast severity and Trails B. No significant moderation existed for other selected tracts, and the effect was not observed with PTSD in place of mTBI. Analysis showed that investigation at the individual-tract level may lead to a deeper understanding of neurological differences between blast and impact injuries.

51. Suicide Risk Profiles Amongst Suicide Exposed U.S. Military Servicemembers and Veterans

Peterson, Amanda [1]; Chen, Jason [2]; Yu, Carol [1]

1. Minneapolis VA Health Care System
2. VA Portland Health Care System

Abstract: Nearly half of all U.S. Military Service members (SMs) and veterans report an exposure to suicide at some point in their lives. This is concerning given that suicide exposure has been associated with a greater risk of suicidal thoughts and behaviors. Further work on identifying those with vulnerability to suicide after suicide exposure is critically needed to inform early detection and facilitate tailored, proactive outreach and intervention strategies. This study utilized latent class analysis (LCA) to examine military SMs/veterans who have been exposed to suicide and identify subgroups of SMs/veterans who are at greater risk for suicidal thinking and behavior. Subgroups were characterized by examining established mental health (e.g., PTSD, depression, anxiety) and suicide-related constructs (e.g., thwarted belongingness, fearlessness about death). Data was obtained from the Military Suicide Research Consortium's (MSRC) Common Data Elements (CDE), which is comprised of 28 MSRC studies who uploaded de-identified CDE for secondary analyses. Results of the LCA indicated three subgroups of SMs/veterans exposed to suicide, two high-risk subgroups and one low-risk subgroup. One high-risk subgroup was characterized primarily by high substance use and traumatic brain injury while the other high-risk subgroup was characterized by greater utilization of behavioral health services, higher anxiety, insomnia, and lower fearlessness about death. How these profiles of risk can inform clinical care and suicide risk management will be discussed.

52. The COPD Frequent Exacerbator Phenotype is Associated with Decreased Sputum Microbiome Alpha Diversity

Pragman, Alexa [1]; Hodgson, Shane [1]; Wu, Tianhua [2]; Zank, Allison [1]; Reilly, Cavan [2]; Wendt, Chris [1]

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

Abstract: RATIONALE: The COPD frequent exacerbator (FE) phenotype is associated with increased morbidity and mortality. Airway colonization with pathogenic bacteria is associated with lung microbiome dysbiosis and pulmonary symptoms. We hypothesized that the upper airway and sputum microbiome of FE is less diverse compared to the microbiome of infrequent exacerbators (IE). Our objective was to identify specific microbiome biomarkers that correlate with FE phenotype. METHODS: iLUMINE is a prospective longitudinal cohort study of the upper airway and sputum microbiome among COPD patients, comparing 40 FE to 40 IE. Exclusion criteria include use of systemic antibiotics or corticosteroids in the previous 1 month. FE was defined as =1 exacerbation in the previous 12 months, and IE were free from exacerbations in the previous 24 months. Subjects provided nasal swab, oral wash, and induced sputum samples at 2 visits separated by 2-4 months. Samples underwent 16S V4 MiSeq sequencing and droplet digital PCR of 16S copies. Data were analyzed using Dada2 and R. RESULTS: FE and IE were well-balanced with respect to age, inhaled corticosteroid (ICS) use, and St. George's Respiratory Questionnaire (SGRQ) score. FE were more likely than IE to have a lower BMI (p=0.022), lower FEV1 % predicted (FEV1pp, p<0.001), and currently use tobacco (p=0.032). Sputum sample a-diversity (Simpson diversity) was decreased among FE samples (linear regression [LR] p=0.0079) and with older age (LR p=0.031). The interaction of FE and age was also associated with decreased sputum a-diversity (LR, p=0.013). FE phenotype and isolation of a pathogen from sputum culture were both associated with decreased a-diversity (LR p=0.019 and p=0.000039, respectively), as was their interaction (linear mixed model, p=0.00001). Oral wash a-diversity increased with higher FEV1pp (LR p=0.018) and decreased with SGRQ score (LR p=0.045). Visit 2 a-diversity significantly correlated with visit 1 values at all sites. When baseline values were included in the model, between-visit COPD exacerbation or antibiotic use was not associated with a-diversity at visit 2. Univariate PERMANOVA analysis of β-diversity demonstrated clustering by anatomic site (all pair-wise comparisons p_{adj}<0.001). FE phenotype (Figure, p=0.029), FEV1pp (p=0.042), pack-years of smoking (p=0.048), and SGRQ score (p=0.041) were associated with β-diversity shifts when site was included in multivariable PERMANOVA.

53. Dorsolateral Prefrontal Cortex Hypoactivation Modulation According to Loss Outcomes in Schizophrenia, but Not Psychotic Disorders More Broadly

Purcell, John [1]; Demro, Caroline [2]; Lahud, Elijah [2]; Burton, Philip [2]; Sponheim, Scott [1-2]

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

Abstract: Psychosis is often characterized by aberrant reward-processing related to atypical emotion expression, diminished pleasure, decreased goal pursuit, and general cognitive impairment in addition to hallucinations and odd beliefs. While those with schizophrenia have demonstrated suboptimal reinforcement learning, previous findings suggest normative processing of pleasant and unpleasant stimuli, suggesting that deficits may lie in how emotional experiences contextualize and affect future behavior. Participants with schizophrenia (n=73), schizoaffective disorder (n=14), bipolar disorder with psychotic features (n=35), first-degree relatives (n=81), and controls without psychosis (n=49) completed the Cued Reinforcement Reaction Time task, including trials of acting to either acquire monetary gains or avoid losses, during fMRI. Behaviorally, the psychosis group demonstrated more response errors than controls, but no reaction-time differences were observed. Brain activation in the bipolar disorder and relative groups did not differ from controls. However, the schizophrenia group demonstrated hypoactivation in the right dorsolateral prefrontal cortex (MNI 32,44,28; k=26 voxels; p<0.02), a region of the brain associated with the integration of reward-relevant information, during loss outcomes according to the amount lost. This prefrontal, cortical activation difference may reflect a deficit in the cognitive comparator process essential for integrating affective responses into coordinated behaviors, rather than the valuative experience of monetary gains and loss associated with subcortical brain structures.

54. Ascertainment of Stroke from Administrative Data to support a Pragmatic Embedded Clinical Trial

Raju, Srihari [1]; McPherson, Jacob [1]; Leatherman, Sarah [2]; Hau, Cynthia [2]; Woods, Patricia [2]; Flynn, Maura [2]; Sadiatis, Christal [2]; Ishani, Areef [1]

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

Abstract: Hospitalization for stroke is based on the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards, which defines stroke as 'the presence of acute infarction as a result from a clinical syndrome as evidenced from symptoms, signs, imaging, laboratory tests, or consistent treatment of symptoms' The goal of this study was to identify stroke hospitalizations using International Classification of Disease (ICD)-10 codes, and use these codes to develop an algorithm, so that human adjudication of charts could be avoided in the future. VINCI was used to pull 9,959 patient charts from within the VA Medical system, and 304 were adjudicated by three reviewers on the study team. This analysis found that the ICD-10 code I61 (Nontraumatic intra cerebral hemorrhage) yielded the highest PPV (100%), and I63 (Cerebral infarction) yielded the second highest PPV (90%). PPV greater than 75% was associated with the codes H34.0-2, I60, I61, I62.9, and I63. Using administrative codes after reliably validating them via manual adjudication has shown that they can be reliably used for purposes such as pragmatic embedded clinical trials. A larger amount of data can be covered with fewer study staff when using an algorithm. It is important to create an accurate algorithm in which the codes are validated to be reliably used on other administrative databases

Research Topic: Clinical Epidemiology
Funding agencies: N/A
Grant support: N/A

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55. Power Assisted Walker: Rising Above Seated Mobility

Ratner, Edward [1-2]; Goldish, Gary [1-2]; Hansen, Andrew [1-2]; Bliss, Jared [1]; Bornstein, A. Soleil [1]; Gustavson, Allison [1]; Morin, Steve [1]; Wacek, Amber [1]

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

Abstract: Nearly half of older people cannot easily walk 400 meters. Powered mobility aids such as seated scooters discourage healthful walking and have limitations due to size and cost. Using human-centered design, we have developed a novel power assisted walker (PAW), which can be used as a manual walker or as a standing electric scooter. A user can push the device manually supported by a four-wheeled walker or step onto a footplate and ride it as a three wheeled standing scooter, with safety enhanced by two anti-tip casters. A working prototype has demonstrated the feasibility of this design. It also meets user-defined requirements for safety, usability, and transportability. Designs for additional prototypes overcome several engineering challenges and will enable a wide variety of users to meet their mobility needs in the community.

Research Topic: Rehabilitative Medicine
Funding agencies: N/A
Grant support: VA Innovation Ecosystem (Spark-Seed-Spread); VA Technology Transfer Program

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56. MATCH: Microbiota or Placebo After Antimicrobial Therapy for Recurrenct *C. Difficile* at Home

Reinink, Andrew [1]; Lehenbauer, Kyle [1]; Anway, Ruth [1]; Belew, John [1]; Nugent, Sean [1]; Shaukat, Aasma [2]; Drekonja, Dimitri [1]

1.   Minneapolis VA Health Care System
2.   VA New York Harbor Healthcare System

Abstract: *Clostridioides difficile* infection (CDI) is the leading cause of infectious diarrhea, with substantial morbidity and mortality. Recurrent infection is especially challenging, with increasing rates of recurrence observed after each previous recurrence, leading to cycles of prolonged symptoms, frequent antimicrobial use, and decreased quality-of-life. Fecal microbiotal transplantation (FMT) is a promising intervention with a large effect size in observational studies, but with conflicting results from randomized controlled trials (RCTs). We are conducting a VA-wide RCT utilizing centralized case identification, with enrollment and FMT administration occurring at the participant's home. This is a RCT of capsule-delivered FMT for the prevention of recurrent CDI, administered after successful initial treatment of recurrent CDI with standard therapy. The primary endpoint is the incidence of recurrent CDI or death. Cases are identified by searching the VA Corporate Data Warehouse, with study coordinators then reaching out to potential participants. Potential participants meeting inclusion criteria and interested in participation are scheduled for in-home consent, randomization, and capsule administration, followed by telephone follow-up for 6 months. To mitigate risks of COVID-19, enrollment via video visits has been implemented. A total of 147 participants have been enrolled through April 2022 from 40 unique states, with 33% being from rural or highly rural areas. Centralized care identification and in-home enrollment is a feasible and innovative method of conducting RCTs in the VA system, improving access to clinical research to populations who may have difficulty engaging with the traditional model of clinical trials enrolling at large hospitals in major metropolitan areas.

Research Topic: Infectious Diseases
Funding agencies: VA CSRD
Grant support: CSP 2004

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57. Examining multiple perspectives to inform the path forward in treatment of phantom limb pain

Rich, Tonya [1-2]; Falbo, Kierra [1-2]; Phelan, Hannah [3]; Krebs, Erin [1-2]; Finn, Jacob [1-2]; Gravely, Amy [1]; Matsumoto, Mary [1-2]; Olney, Christine [1-2]; Kiecker, Jessica [1]; Hansen, Andrew [1-2]

1.   Minneapolis VA Health Care System
2.   University of Minnesota
3.   Medical College of Wisconsin

Abstract: Phantom limb pain (PLP) commonly occurs after amputation with an unknown mechanism, making this type of pain challenging for clinicians to treat and patients to manage. Several research projects are currently being conducted to examine perspectives on PLP experiences, challenges, and interventions from the point of view of multiple stakeholders. The objective of these efforts is to inform the research path forward in developing novel, effective PLP treatments that are practical and build upon best clinical practices. To better understand PLP, we studied the perspectives of 1) Veterans and 2) VA clinicians. Additionally, we conducted 3) a review of the literature and 4) neuroimaging. 1) We used phone interviews to obtain qualitative data on the Veterans' experiences with amputation and characterize this sample using clinically available pain outcome measures. 2) We used an online survey with VA amputation clinicians nationally to understand their perspectives on PLP evaluation and treatment. We asked additional questions on non-drug PLP treatments, including 3-phase Graded Motor Imagery (GMI). 3) We are conducting a scoping review of the literature on the evidence for GMI in treating PLP. 4) We are conducting a neuroimaging pilot study to understand brain activity differences between Veterans with PLP and Veterans without PLP. Qualitative interviews with 50 Veterans with amputations led to the identification of the following themes: high variability of the PLP experience and familiarity with PLP treatments. Pain outcome measures demonstrated acceptable internal consistency. Survey data from 73 VA amputation clinicians suggested that there is limited use of pain outcome measures. Clinicians identified specific characteristics (e.g., mindset, motivation, commitment) can facilitate patient success with GMI treatment for PLP, however, not all patients fit these ideal characteristics. The current literature for GMI treatment showed variation in the number of GMI phases used and dosing of the treatment across 38 studies. Recruitment is ongoing for the neuroimaging study with 8 completed data sets to evaluate differences in brain activation. PLP is complex and variable. The effectiveness of non-drug treatments for PLP after amputation is not well studied. Considering the perspectives of both the patients and the clinicians on their experience with PLP and treatments will inform both the direction of our research and development of potential future interventions.

Research Topic: Rehabilitative Medicine
Funding agencies: VA RRD
Grant support: IK1RX003216

58. The Effects of Theta Burst Stimulation on Veterans with Traumatic Brain Injuries and Chronic Headaches

Saladin, Katrina [1]; Krueger, Alyssa [2]; Vogsland, Rebecca [1]; Lim, Kelvin [1-2]; Armstrong, Michael [1]; Gilmore, Casey [1]; Macedo, Franz [1]; Albott, C. Sophia [2]

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

Abstract: Chronic headache is the most debilitating clinical symptom in individuals who have suffered a mild traumatic brain injury (mTBI). Unfortunately, the debilitation caused by headaches is often accompanied by dysfunction in mood, attention, and memory which results in a profound negative impact on these individuals' quality of life. Conventional pharmacological treatments have been shown to be ineffective in alleviating headaches in the posttraumatic injury population. Currently, there are no FDA-approved treatments for posttraumatic headache. The primary objective of this open label pilot study is to investigate the safety and efficacy of theta-burst stimulation (TBS) for the management of posttraumatic headache, thereby improving outcomes and quality of life for those who have suffered a TBI. We hypothesized that accelerated TBS would 1) be safe and well tolerated, 2) reduce the intensity and frequency of headaches 3) improve function and quality of life outcomes, and 4) produce durable improvements in outcome measures. Participants completed 2 weeks of pre-intervention assessment via daily Ecological Momentary Assessment (EMA). The EMA is a software that sends participants surveys to their personal phones that assess their behaviors and headache symptoms in real-time. Participants were required to complete at least 50% or more of the EMA questions prior to initiation of the TBS intervention. They then received TBS three times a week for four weeks while continuing to fill out the EMA questions. After the TBS intervention, participants completed 4 additional weeks of EMA and returned for a 1-month follow-up assessment. To date, our pilot sample has shown significant improvement in three areas: 1) intensity of headaches which persisted over the follow-up period, 2) impairment associated with headaches and 3) quality of life measures after completing a course of accelerated TBS.

Research Topic: Traumatic Brain Injury (TBI)
Funding agencies: CVRE
Grant support: Minnesota Office of Higher Education SWIFT Contract No. 159883

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59. Inhibition of Mitochondrial Antioxidant Defense and CDK4/6 in Mesothelioma

Scaria, George [1]; Kratzke, Marian [1]; Porter, Stephen [1]; Kren, Betsy [1]; Klein, Mark [1]

1.   Minneapolis VA Health Care System

Abstract: Mesothelioma is a devastating and recalcitrant cancer that arises from the pleura or lining of the peritoneum. Treatment for advanced mesothelioma may include chemotherapy or immunotherapy with checkpoint inhibitors. However, mesothelioma is incurable in the majority of cases and new treatment strategies are needed. Two pathways that show promise but remain to be significantly studied include mitochondrial antioxidant defense (MAD) and the cell cycle. We hypothesized that select cell cycle-related proteins may compensate for inhibition of one part of the cell cycle machinery and targeting the MAD system might ac synergistically in combination with CDK4/6 inhibition. METHODS. Inhibition of CDK4/6 with palbociclib (PD) or MAD using auranofin (AU) were evaluated for activity against mesothelioma cells in vitro for cell proliferation and colony formation. PD and AU were evaluated at several concentration combinations in cell proliferation assays to determine if the combination was additive or synergistic. Combination indices (CI) were calculated via the Chou-Talalay method. Immunoblotting was used to evaluate expression of key survival proteins after treatment with PD or AU as well as cell cycle effects by FACS. RESULTS. ICS0s at 72 hrs were determined to be 7μM, 7μM, 18μM and 13μM for PD; 4μM, 3μM, 4μM and 3μM for AU in mesothelioma cell lines H2052, H2373, H2452, and H2461, respectively. Colony formation was decreased after 72 hrs incubation with 5 μM PD in Ba pl-expressing (28%; 55%) or AU (4%, 13%) and Ba pl-null cell lines with PD (59%; 65%) and AU (11%; 4%) versus untreated controls. CI<1 (denoting synergism) was identified for several combinations of AU and PD for cell lines evaluated. Treatment for 72 hrs with 1.25 μM AU resulted in loss of FoxMl expression, pro-survival survivin and decreased expression of Mcl-1 and Bcl-xL, as well as CDKs 4/6 and Rb. PD at lx the ICS0 concentration decreased expression of FoxMl, pro-survival survivin, Mcl-1 and less so Bcl-xl. PD increased expression CDK4/6 partner cyclin Dl, as well as cyclin E, CDK2 and Rb. PD caused cells to accumulate in Gl phase while AU increase the sub-Gl population indicative of apoptosis. CONCLUSIONS. Auranofin and palbociclib were effective in decreasing cell growth and inhibiting the above-described activity across all assays. Further study of this drug combination will elucidate the contribution o these pathways to mesothelioma activity and may reveal a new treatment strategy.

Research Topic: Cancer
Funding agencies: VA BLRD
Grant support: I01BX004655

60. Neural and behavioral predictors of maladaptive avoidance in young military recruits

Schmit, Jennifer [1-2]; Marquardt, Craig [1-2]; Davenport, Nicholas [1-2]; Lissek, Shmuel [2]; Lim, Kelvin [1-2]; Polusny, Melissa [1-2]

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

Abstract: Fear generalization during Pavlovian conditioning is associated with clinical anxiety and may impact everyday decision-making when people are faced with competing incentives and threats in their environments. For some individuals, maladaptive and unnecessary behavioral avoidance can result. The connection between brain markers of Pavlovian fear generalization and later avoidance is poorly understood. Further understanding is particularly applicable to military personnel within high-risk environments where threat-based decision-making is prevalent. We administered an event-related fMRI fear-generalization paradigm, which was embedded in a computer game during which various shapes appeared on the screen. Extreme shape sizes served as cues of conditioned-danger (CS+) or conditioned-safety (CS-). CS+ cues were paired with a mild electric shock. Other resembling shapes, presented in the absence of shock, served as generalization stimuli (GSs). During the game, participants chose whether to avoid the shock at the cost of poorer performance. Avoidance during GSs is considered maladaptive because shock is not a realistic prospect and thus unnecessarily compromises performance. We observed expected generalization gradients in threat salience-related brain regions which interacted with 'wanting-to-win' ratings to predict maladaptive generalized avoidance. Within the dmPFC (p=0.004, .p2=0.170), right insula (p=0.031, .p2=0.101), and left insula (p=0.031, .p2=0.102), increased reactivity to GSs predicted more maladaptive avoidance only when participants' desire to win was low. This study highlights the role of fear generalization in predicting maladaptive avoidant behaviors. Greater activation of the salience network may produce avoidance specifically when approach motivation is low. Laboratory brain markers of generalized fear-avoidance relations hold promise for understanding longitudinal outcomes and resilience-related decision-making among military populations.

Research Topic: Behavioral Sciences
Funding agencies: NIH
Grant support: NCCIH UH3AT009651

61. Innovation at the VA - The Prosthetic Sock Management Tool

Slater, Billie [1]

1. Minneapolis VA Health Care System

Abstract: Acknowledging the importance of pre-, post- and rehabilitative care for people having an amputation, in 2017 the VA and DOD together issued revised clinical practice guidelines for rehabilitation of individuals with lower limb amputations. These guidelines recommend that physical and functional interventions for prosthetic training be provided to patients. This includes residual limb management, which incorporates instruction on the correct the donning and doffing of prosthetic socks. The Prosthetic Sock Management Tool (PSMT) is a two-piece instructional system that clinicians may use for this purpose. The PSMT consists of an easy-to-use three zippered pouch system with labeled pouches and a laminated instructional infographic. The PSMT project began in 2018 as a VHA/VA Innovator's Network supported project in the Minneapolis VA Health Care System. With input from a broad variety of stakeholders (including Veterans, Physiatrists, Prosthetists, Rehabilitation Therapists, and others) human-centered design principles were put into action. Information sharing sessions were held. Prototypes and their iterations soon followed. After a small pilot test at the Minneapolis VA, with the support of the National Program Manager of the Amputation System of Care (ASoC), the PSMT was introduced on a national call of the VA Amputation Rehabilitation Coordinators (ARCs). There was great interest in this new instructional material. Due to the COVID-19 pandemic, professional manufacturing of the PSMT was delayed by one year. As a pivot, the instructional infographic (both still and animated) was able to be deployed to over 12 VA facilities and is currently in use. Data was collected to measure clinician satisfaction with its use. One hundred percent of the clinicians polled said that they would recommend the PSMT Infographic to a colleague! As production resumed and material supplies became available, 200 PSMT units were produced with the support of the Innovators Network (iNET) and the Technology Transfer Assistance Program (TTAP). The PSMT system was recently deployed to 26 facilities within the VA ASoC. Nearly 90% of Amputation Rehabilitation Coordinators surveyed would recommend the PSMT to their friends or colleagues. One hundred percent of the ARCS would like to order more units to use with their patients. This project gives our VA clinicians a novel instructional material to support patient education on a crucial topic for the health and comfort of our Veterans.

Research Topic: Prosthetics
Funding agencies: N/A
Grant support: Technology Transfer Assistance Program and Innovators Network

62. **Microglial FABP4-UCP2 Axis Modulates Neuroinflammation and Cognitive Decline in Obese Mice**

So, Simon [1]; Fleming, Kendra [1]; Nixon, Joshua [1,3]; Duffy, Cayla [1]; Bernlohr, David [3]; Butterick, Tammy [1,3]

1.   Minneapolis VA Health Care System
2.   Center for Veterans Research & Education
3.   University of Minnesota

Abstract: The microglial fatty-acid-binding protein 4-uncoupling protein 2 (FABP4-UCP2) axis is a key regulator of neuroinflammation in high-fat-diet (HFD)-fed animals, indicating a role for FABP4 in brain immune response. We hypothesized that the FABP4-UCP2 axis is involved in regulating diet-induced cognitive decline. We tested cognitive function in mice lacking microglial FABP4 (AKO mice). Fifteen-week-old male AKO and wild-type (WT) mice were maintained on 60% HFD or normal chow (NC) for 12 weeks. Body composition was measured using EchoMRI. Locomotor activity, working memory, and spatial memory were assessed using behavioral tests (open field, T-maze, and Barnes maze, respectively). Hippocampal microgliosis was assessed via immunohistochemical staining. An inflammatory cytokine panel was assayed using hippocampal tissue. Real-time RT-PCR was performed to measure microglial UCP2 mRNA expression. Our data support that loss of FABP4 prevents cognitive decline in vivo. HFD-fed WT mice exhibited impaired long- and short-term memory, in contrast with HFD-fed AKO mice. HFD-fed WT mice had an increase in hippocampal inflammatory cytokine expression (IFNγ, IL-1β, IL-5, IL-6, KC/GRO, CXCL1), IL-10, and TNFα) and microgliosis, and decreased microglial UCP2 expression. HFD-fed AKO mice had decreased hippocampal inflammatory cytokine expression and microgliosis and increased microglial UCP2 expression compared to HFD-fed WT mice. Collectively, our work supports the idea that the FABP4-UCP2 axis represents a potential therapeutic target in preventing diet-induced cognitive decline. Relevance to Veteran health care: Obesity and associated comorbities such as metabolic syndrome and diabetes affect up to 48% of Veterans and are known risk factors for cognitive impairment and development of Alzheimer's disease. The incidence of these neurodegenerative diseases may be higher in Veterans than in the general population.

63. **Relationship of Self-Determined Motivation with Work Behavior and Response to Cognitive Remediation for Individuals with Schizophrenia**

Spann, Desmond [1]; Nienow, Tasha [1]

1.   Minneapolis VA Health Care System

Abstract: Deficits in motivation have been found to be prevalent among individuals with schizophrenia. Research has shown that these deficits are associated with poorer functional outcomes, and consequently, they have become an important concept to examine. The primary aim of this study was to examine the relationships between motivation, observed work behavior, and response to cognitive remediation therapy. Participants were 74 outpatients with schizophrenia who attended a 48-session cognitive remediation training program. They attended 3 sessions a week at the Minneapolis VAHCS and were paid for their attendance at sessions. The Treatment Self-Regulation Questionnaire (TSRQ) was used to measure motivational orientation (autonomous, controlled, amotivation) pre- and post-intervention. Participant motivation during the intervention and instructor-observed work behavior was measured with the Intrinsic Motivation Inventory (IMI) and the Work Behavior Inventory (WBI) at 3, 9, and 16 weeks of intervention. Response to treatment was measured with performance on the Overall Composite on the MATRICS Consensus Cognitive Battery (MCCB) and training gains on a word N-back task. Participants reported a relatively high level of autonomous motivation as compared to controlled motivation or amotivation at baseline and post-intervention assessments. As expected, autonomous and relative autonomous motivation (amount of autonomous motivation present in comparison to controlled motivation) were positive correlated with multiple aspects of self-reported intrinsic motivation during the intervention. Controlled motivation was unrelated to most aspects of self-reported intrinsic motivation, while amotivation, defined as a lack of intention, was inversely related to aspects of intrinsic motivation. Motivation was associated with observed work behavior during training. Autonomous and relative autonomous motivation was positively correlated with observed work behavior, while inverse relationships were observed with controlled motivation and amotivation. Interestingly, relative autonomous motivation most consistently related to observed work behavior and was the only aspect of motivation positively related to change in treatment. In contrast, inverse relationships were found between control motivation and change in treatment. Results suggest that addressing these motivational orientations prior to treatment could improve outcomes.

64. CSP 2014: Comparative Effectiveness of Two Formulations of Buprenorphine for Treating Opioid Use Disorder in Veterans (VA BRAVE)

Swanson, Heather [1]; Dickmann, Patricia [1]; Steen, Katie [1]; Westermeyer, Joseph [1]

1.   Minneapolis VA Health Care System

Abstract: CSP 2014 (Comparative Effectiveness of Two Formulations of Buprenorphine for Treating Opioid Use Disorder in Veterans (VA-BRAVE)) is part of VA's initiative to improve healthcare, and specifically improve treatment for veterans with opioid use disorder (OUD). The purpose of this study is to understand whether buprenorphine given in a monthly injection form works similarly to or better than buprenorphine taken daily in an oral form (the standard of care) and determine if one of the two forms is better at helping Veterans stay in treatment for OUD and limit their drug use behaviors. This is a large, open-label and randomized nation-wide trial that will include ~900 male and female veteran patients from ~20 VA medical centers across the country. Secondary goals of the study are to examine comorbid substance use, fatal and non-fatal overdose, HIV and HCV testing results and risk behaviors, incarceration, quality of life, psychiatric symptoms of depression and posttraumatic stress disorder, housing status, and cost-effectiveness. Participants have a 50:50 chance of receiving one of the two forms of buprenorphine. All participants start receiving oral buprenorphine, then are randomized and will receive either a 28 day supply of sublingual buprenorphine or come in and receive an injection every 28 days at study visits. Active participation will last for 1 year and involves weekly study visits for the first 4 weeks then study visits every two weeks until the end of 52 weeks. Study visit activities include periodic blood draws (e.g. hepatitis panel, HIV, liver function tests, blood buprenorphine levels), EKG, a physical exam, and each study visit will involve a urine sample to test for opioids, pregnancy test, medication management, and questionnaires and clinical interviews.

Research Topic: Drug Dependence
Funding agencies: None
Grant support: N/A

65. Diuretic Comparison Project (DCP): Participating Provider Experiences

Taylor, Olivia [1]; Ikeri, Eustacia [1]; Majkut, Alison [2]

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

Abstract: The Diuretic Comparison Project is a large-scale, national, centralized comparative effectiveness clinical trial. The study compares the effects of hydrochlorothiazide (HCTZ) versus chlorthalidone (CTD) on cardiovascular outcomes. Primary care providers (PCPs) were consented as study participants, allowing the study to contact their patient panels. When a patient consented to participate, their PCP was contacted again to approve randomization to either HCTZ or CTD. To better understand providers' motivations, decision making processes, and attitudes towards the DCP, we conducted interviews with a sample of participating PCPs in the Minneapolis VA Healthcare System. PCPs were invited for interviews by a series of email blasts from the study email account, along with announcements at staff meetings. A total of 161 providers consented to the DCP from the MVAHCS. After removing those who no longer worked for the VA, 103 were emailed interview invitations. Semi-structured interviews were conducted over Microsoft Teams using a prepared interview guide. Ultimately, 8 PCPs were interviewed, consisting of 1 NP and 7 MDs. These PCPs listed their interest in clinical research, desire to learn the results of the DCP, and the involvement of the DCP's late principal investigator, Dr. Frank Lederle, among their reasons for joining the study. Their experiences participating as providers were overwhelmingly positive. Most PCPs said the patient-informed consent process and interchangeability of HCTZ and CTD contributed to their decisions to approve randomizations. Reasons PCPs declined randomization included concerns about patients developing hypokalemia on CTD, worries about patient adherence to a new medication, the realization that thiazides were not indicated for a patient, and deciding to switch patients to CTD. Some PCPs indicated they had no reason to decline consented patients. These interviews provided valuable insight into the perspectives of PCPs involved in the DCP. However, the data collection was limited both in volume and scope, as only 8 providers were interviewed from one DCP study site. In order to build upon these findings, we intend to disseminate a survey to all providers who have participated in the DCP, including sites beyond the Minneapolis VA. We will also examine documented feedback from providers that has accumulated throughout the lifetime of the DCP.

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

66. Targeting genetics for pressure injury prevention in Veterans with spinal cord injuries: A multi-site and interdisciplinary biomarker study

Toth, Anna [1]; Kemmer, Sara [1]; Bogie, Kath [2]; Alvarado, Nannette [2]; Henzel, M. Kristi [2]; Richmond, Mary Ann [2]; Schwartz, Katie [2]; Srinivasan, Meghna [2]; Graves, Letitia [2-3]; Galea, Marinella [4]; Tisi, Amelia [4]; Simelane, Johane [4]; Escoto, Kathleen [4]; Graham, Ilda [4]; Olney, Christine [3]

1. Minneapolis VA Health Care System
2. Louis Stokes Cleveland VA Medical Center
3. University of Texas Medical Branch
4. James J. Peters Department of Veterans Affairs Medical Center

Abstract: Pressure injures (PrI) are a major secondary complication for many people with spinal cord injury (SCI). Development /or recurrence of a PrI limits activities of daily living, often leading to hospitalization and even death. PrIs have a devastating impact on affected individuals and their caregivers. The economic burden of PrI remains significant, both for the Veteran and for VA hospitals that provide lifetime care for our Veterans with SCI. This study is addressing the conundrum of why some Veterans with SCI suffer from a continuous cycle of recurring PrI, while others remain PrI free. This Dept of Veterans Affairs Rehabilitation R&D funded (Grant #: RX003081) study builds upon Dr. Kath M. Bogie's BEIPIR model (Biomarkers for Early Identification of Pressure Injury Risk) for persons with SCI. This model found that persons with SCI can sometimes exhibit rapid intramuscular adipose tissue (significant risk factor for PrI) and others do not, which gave rise to this study's central hypothesis: DNA variants predispose some individuals to PrI risk. Participants visit once a year for a blood draw (to observe changes in DNA/biomarkers) and CT scan of the pelvic region (to observe changes in muscle composition of the sitting area). Veterans are followed up with monthly for a skin health questionnaire to monitor for PrI. Total study enrollment from the three VA sites will be 100 veterans (primary site is at Louis Stokes VA Medical Center Cleveland, Ohio [Kath M. Bogie, PhD Phil, PI] Cleveland, Ohio; second site is James J. Peters VA Medical Center, Bronx, NY [Marinella Galea, MD, Site PI]). The Minneapolis VA site (Christine Olney, PhD RN Site PI) will enroll fifteen, for which we have currently enrolled three Veterans. We will continue to recruit and enroll the other twelve over the next several months. Together we will discover the relationships of muscle composition with genetic variation, which we believe will better identify individuals who may require a higher level of early, proactive PrI prevention. Our participation in this study aligns with our SCI/D Center's initiatives to better target PrI prevention processes for our Veterans with SCI. Further, in the longer term, this research has the potential to have a broader impact by leading to development of a clinical or even home-testing kit for identifying PrI risk.

67. Investigation of a new role for protein kinase CK2 in prostate cancer progression

Trembley, Janeen [1-2]; Kren, Betsy [1-2]; Risk, Michael [1-2]; Peltola, Justin [1-2]; Iwamoto, Carlos [1-2]; Li, Yingming [2]; Dehm, Scott [2]; Klein, Mark [1-2]; Ahmed, Khalil [1-2]

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

Abstract: A significant unmet need exists for patients diagnosed with advanced prostate cancer (PCa) who have a poor prognosis after not responding to first line initial therapy. Metastatic PCa is lethal with a 5-year survival rate of about 30%. Drugs targeting the androgen hormone/androgen receptor axis have been the mainstay of second line treatment for advanced disease since 2011. Only 25-30% of patients who progress on the first drug respond to the second drug, with a short-term progression free survival of ~3 months. Further, second line drugs are now incorporated simultaneously along with standard initial therapy in patients who present with metastatic PCa, limiting drug options since this treatment regimen can also fail. Thus, finding new combination drugs and better treatment options for advanced forms of PCa remains an urgent clinical need. Cancer is characterized by unchecked cell proliferation and avoidance of cell death. Our focus is on a cellular signal called 'protein kinase CK2' which we identified as a major regulator of PCa cell survival. CK2 levels are higher in PCa than in normal prostate cells. High CK2 levels in PCa patient tumors is associated with worse disease status and shorter survival. In laboratory experiments, high CK2 levels obstruct death in PCa cells; conversely, blocking CK2 function kills human PCa cells grown in culture and as tumors in mice. Recently, we discovered that current androgen-blocking treatments cause higher CK2 expression in PCa. Importantly, we found that blocking CK2 activity promoted cell death in drug-resistant PCa, and dramatically improved response to Abiraterone (a current clinical therapy). This suggests that CK2 might be an effective therapeutic target for preventing or overcoming anti-androgen drug resistance. We propose that treatment-induced elevation of CK2 is an underlying cause of anti-androgen drug resistance. Currently investigations center on how CK2 elevation alters cancer cell signaling and response to androgen pathway drugs. Military personnel have increased PCa incidence (2-fold). Safe drugs to block CK2 exist - one is currently in clinical trials for other cancer types (Silmitasertib or CX-4945). As we continue these investigations, our findings could rapidly translate into a clinical trial within the VA healthcare system, representing a potential breakthrough for PCa treatment in Veterans and other patients.

68. Preclinical model of U.S. military burn pit exposure

Trembley, Janeen [1-2]; So, Simon [1,3]; Fleming, Kendra [1-2]; Bowdridge, Elizabeth [4]; Garner, Krista [4]; Griffith, Julie [4]; Engles, Kevin [4]; Batchelor, Thomas [4]; Goldsmith, William [4]; Hussain, Salik [4]; Nixon, Joshua [1-2]; Nurkiewicz, Timothy [4]; Butterick, Tammy [1-2]

1. Minneapolis VA Health Care System
2. University of Minnesota
3. Center for Veterans Research & Education
4. West Virginia University

Abstract: Objective: Chronic multisymptom illness (CMI) is an idiopathic disease affecting thousands of U.S. Veterans exposed to open-air burn pits emitting aerosolized particulate matter (PM) while serving in Central and Southwest Asia and Africa. Exposure to burn pit PM can result in profound biologic consequences including chronic fatigue, impaired cognition, and respiratory diseases. Dysregulated or unresolved inflammation is a possible underlying mechanism for CMI onset. We describe a rat model of whole-body inhalation exposure using carbon black nanoparticles (CB) as a surrogate for military burn pit-related exposure. Using this model, we measured biomarkers of inflammation in multiple tissues. Results: Male Sprague Dawley rats were exposed to CB aerosols by whole body inhalation (6 ± 0.83 mg/m3). Proinflammatory biomarkers were measured in multiple tissues including arteries, brain, lung, and plasma. Biomarkers of cardiovascular injury were also assayed in plasma. CB inhalation exposure increased CMI-related proinflammatory biomarkers such as IFNγ and TNFα in multiple tissue samples. CB exposure also induced cardiovascular injury markers (adiponectin, MCP1, sE Selectin, sICam1 and TIMP1) in plasma. These findings support the validity of our animal exposure model for studies of burn pit-induced CMI. Ongoing studies include more complex toxicant mixtures documented at multiple burn pit sites that include polycyclic aromatic hydrocarbons (PAH) or volatile organic compounds (VOC) such as naphthalene (NA). Significance to Veterans Health Care: A proper understanding of the physiological dysfunctions that follow burn pit exposure is essential to future discovery of diagnostic measures and evidence-based treatments. Our model provides a necessary tool for reproducible and systematic investigations, including future studies using even more complex toxicants present at various burn pit sites. Validation of this model is a crucial and necessary step in identifying and ameliorating the adverse health effects associated with burn pit exposure-induced CMI. Keywords: Burn Pit Exposure, Chronic Multisymptom Illness, Inflammation, Cytokines, Environmental Exposure, Inhalation toxicology, Nanoparticle, Carbon Black

69. Risk and Protective Factors Across Socioecological Levels of Risk for Suicide: An Evidence Map

Ullman, Kristen [1]; Landsteiner, Adrienne [1]; Linskens, Eric [1]; MacDonald, Rod [1]; McKenzie, Lauren [1]; Murdoch, Maureen [1]; Sayer, Nina [1]; Stroebel, Benjamin [1]; Sultan, Shahnaz [2]; Venables, Noah [1]; Wilt, Timothy [1]

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

Abstract: Introduction: Suicide rates in United States military populations are high. Adjusted suicide rates among US veterans are 1.5 times the general population. We conducted a systematic review and prepared an evidence map of risk and protective factors in general, average-risk populations of US veterans and active-duty military to help identify priorities for future research Materials and Methods: We searched EMBASE, Medline, PsychINFO, and Sociological Abstracts to identify articles published between 2011 and February 2021. We included randomized-controlled trials, prospective cohort, retrospective cohort, cross-sectional, and case control studies. The Quality in Prognosis Studies Risk of Bias tool was used to measure study risk of bias. We grouped risk and protective factors according to the Social-Ecological Model and created an evidence map. Results: Sixty-three studies met inclusion criteria; 55 of which were rated as low or moderate risk of bias Most studies were retrospective cohorts (k=41), 7 were prospective cohorts, 50 reported individual factors, 22 reported relational factors, 3 reported community factors, and 0 reported societal factors. Information on suicide risk factors came mainly from moderate risk of bias retrospective cohort studies and focused on the individual-level domain of the Social-Ecological model. Evidence was limited due to risk of bias, small number of prospective studies, differences in risk factor definitions, and failures to control for confounding. However, information from prospective cohort and low risk of bias studies indicated that a history of prior suicide ideation or attempts, depression/anxiety, and substance, alcohol, or tobacco use are consistently predictive of, or associated with, suicide deaths and attempts. PTSD was not consistently associated with suicide. Conclusions: While several risk and protective factors were associated with suicide, additional research is needed to better identify at-risk individuals and develop prevention strategies according to socio-ecological levels of suicide risk.

70. Episodic Rehabilitation in Chronic Lower Limb Loss: Revisiting Rehabilitation Potential

Wacek, Amber [1]; Looft, John [1-2]; Cave, Juan [1]; Sauerbrey, Matthew [1]

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

Abstract: Persons living with lower limb loss have persistent issues with balance, falls, and mobility even after prescription of a prosthesis and initial period of rehabilitation. Episodic rehabilitation in chronic lower limb loss has the potential to address some of these mobility concerns but has minimal literature to support further intervention. The goal of this report is to explore the potential of rehabilitation on mobility and balance in persons with chronic lower limb loss. Veterans with lower limb loss and a definitive prosthesis were enrolled in the study looking at measuring mobility using a phone application with a period of personalized rehabilitation intervention for 3 months. Physical and subjective outcome measures were completed prior to and after intervention period. Veterans (n=2) enrolled in the study at baseline did not meet their prescribed K-level, a measure of their functional community/home mobility, and were assigned interventions. K-level was established by physical performance measures, average daily step count and assistive device reliance by expert consensus. Both participants were 3+ years post amputation. Subject 1 (63yo, 12 physical therapy sessions, 6 Motivational Interviewing sessions) improved beyond the Minimally Detectable Change (MDC) on the Six Minute Walk Test, and the Four-Square Step Test following intervention. Subject 2 (51yo, 8 physical therapy sessions, 7 Motivational interviewing sessions) improved beyond the MDC on Berg Balance Scale, Functional Gait Assessment, Four-Square Step Test, and Amputee Mobility Predictor. Both participants improved significantly in subscales of the Prosthetic Evaluation Questionnaire, a subjective questionnaire. These results imply some responsiveness to interventions for balance and mobility even years after an amputation and aid in confirming that there are ongoing impairments that limit mobility in those with chronic lower limb loss. Additionally, these results, support further investigation into the effects of intervention on mobility levels in chronic lower limb loss.

71. The Phenomenon of Prosthetic Socket Fit: What Providers Think

Walker, Nicole [1]; Bornstein, Alexandra [1]; Kemmer, Sara [1]; Falbo, Kierra [1]; Ferguson, John [2]; Fairhurst, Stuart [1]; Voss, Greg [1]; Hansen, Andrew [1]; Olney, Christine [1]

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

Abstract: The volume of a lower extremity residual limb fluctuates daily and over time. The prosthetist fabricates the prosthetic socket to accommodate the shape and volume of the limb, but volume fluctuations throughout the day can affect prosthetic socket fit. A poorly fitting socket can cause skin problems, including shear wounds, ulcers, and calluses. If untreated, these skin irritations can become infected, potentially causing pain, surgical intervention, or reduced participation. Prosthetic socks are commonly used to manage volume fluctuation and socket fit–the patient adds or subtracts prosthetic socks to accommodate changes and improve fit. When used properly, prosthetic socks are an inexpensive and effective means of managing volume. Prosthetists and patients agree that poor socket fit is a significant problem, but many patients have difficulty managing volume. Thus, the focus of this project was to gather information from VA prosthetists regarding clinical facilitators and barriers to volume management among lower-extremity prosthesis users. VA prosthetists were recruited to participate in virtual focus groups. Qualitative and quantitative methodologies were used to understand prosthetists' perspectives on topics including the extent of socket fit issues, sock use training methods, and other barriers and facilitators to volume management. A rapid-turnaround method was used to analyze qualitative data, and descriptive statistics were used to analyze questionnaire data. Six (n=6) certified prosthetists from six VA sites participated. Three focus groups with two prosthetists each were conducted from 12/9/2021 to 12/21/2021. Fourteen qualitative domains were established. Analysis revealed consensus among VA prosthetists in several the domains, but there remains variation in practice among clinicians. Key highlights from qualitative analysis include: prosthetists estimate as many as 95% of their patients use socks to manage volume; between a quarter and a half of patients wear the incorrect number of socks when seen by the prosthetist; new and experienced users alike don't always understand or react to indicators that signal a change in sock ply is needed. The results of this study will be used to inform VA clinicians of the scope of volume management problems prosthetists face, which will contribute to improved training methods, encourage interdisciplinary volume management solutions, and advise the development of technologies for socket fit.

72. CSP 2016: National Adaptive Trial for PTSD related Insomnia

Westermeyer, Joseph [1]; Swanson, Heather [1]

1.   Minneapolis VA Health Care System

Abstract: VA Cooperative Studies Program (CSP) #2016 (National Adaptive Trial for PTSD related Insomnia (VA NAP)) is a double-blind, four-arm adaptive clinical trial to compare the efficacy of trazodone hydrochloride, eszopiclone, and gabapentin to placebo, as adjunctive therapies in the treatment of insomnia symptoms among veterans with military related PTSD, as measured by statistically significant difference in change from baseline in Insomnia Severity Index (ISI) total score at Week 12. For adequate power, this study plans to randomize ~1200 Veterans across ~34 sites nation-wide. The Insomnia Severity Index (ISI) is the primary outcome measure for this study. Other secondary outcome measures will measure change in PTSD symptoms, sleep, comorbid depression, anxiety, quality of life, treatment satisfaction questionnaire for medication, smoking and alcohol consumption, clinical global change, resource utilization, as well as safety measures such as a Suicide Screening Questionnaire, review of Adverse events, and measuring anger and aggression. Participants will be male and female veterans with PTSD and at least moderate levels of insomnia as measured on the ISI at baseline/screening. Veterans who meet inclusion and exclusion criteria will be randomized within each site to receive trazodone hydrochloride, eszopiclone, gabapentin or placebo. A mid-point interim analysis will be conducted wherein active treatment arms meeting early futility stopping criteria may be dropped. Study drug dose will ideally be increased using a flexible dose titration schedule over the initial 3-week period, and the maximally tolerated dose will be continued until the week 12 assessment. Overall, the study duration for each participant is roughly 4.5 months, 12.5 weeks of which patients are taking the study medication.

73. Facing Fragmented Care: Rural Primary Care Provider Perspectives on Evidence-Based Management of COPD among Veterans

Wilson, Talitha [1]; Dudley, Adams [2]; Baldomero, Arianne [2]

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

Abstract: Chronic obstructive pulmonary disease (COPD), a leading cause of disability and death in the U.S, disproportionately affects rural communities. Rural counties experience more COPD-related hospitalizations and deaths than urban counties. Reasons for these disparities likely include challenges in delivering evidence-based COPD management. We aimed to assess barriers, facilitators, and recommendations to the provision of evidence-based COPD management in rural clinics. A qualitative study was performed using semi-structured interviews of primary care providers (PCPs, n=12) managing patients with COPD in rural clinics across five Midwest states. PCPs were drawn from the Veterans Health Administration (VA) Midwest Health Care Network. Transcribed interviews were coded using directed content analysis. Key barriers to evidence-based practice in rural clinics from a PCP's perspective included competing priorities and limited resources. Most PCPs expressed frustration in the coordination of care required for non-VA referrals for spirometry and pulmonary care. Given these challenges, PCPs alluded to difficulty applying guidelines in practice and maintaining continuity of care. Facilitating factors to the delivery of evidence-based COPD management included multidisciplinary clinical support, appointment availability, and options for tobacco cessation intervention. Clinicians recommended increasing access to pulmonary specialty care and the development of an electronic health record (EHR) clinical decision support tool for COPD. There was consensus that a COPD disease management program would improve access to specialty care and adherence to evidence-based management. Further research should evaluate patient perspectives on evidence-based COPD care. Rural-urban disparities in COPD may be mitigated through disease management programs, leveraging EHR for decision support, and increasing access to pulmonary specialty care.

73. Health Disparities between Rural and Urban Veterans with COPD in the COVID-19 Era

Zanotto, Alexander [1]; Baldomero, Arianne [1]; Michalik, Michael [1]; Wendt, Christine [1]

1.   Minneapolis VA Health Care System

Abstract: RATIONALE Veterans have a high prevalence of COPD putting them at increased risk for complications during the COVID-19 pandemic. In addition, more than 30% of Veterans reside in rural areas where the incidence of COVID-19 has been generally higher and mitigation efforts have been lower. Our goal was to determine if there are urban-rural differences in COVID-19 mitigation practices, vaccination willingness, and respiratory and mental health in Veterans with COPD. METHODS We recruited Veterans with COPD, defined as FEV1/FVC ratio <70, for a single survey. Rural and urban cohorts were determined by the primary mailing address. The survey contained 121 questions pertaining to respiratory health, access to healthcare, mental health, COVID-19 mitigation practices, vaccination history, and individuals' perception of the benefit of vaccines. The survey consisted of validated survey tools (COPD Assessment Test (CAT), Patient Health Questionnaire (PHQ)-4 and the Perceived Stress Scale (PSS)-4 Short Form). We evaluated the associations between rurality and outcomes measures using chi-square test for categorical variables or t-test for continuous variables. RESULTS Participants consisted of 31 rural and 36 urban Veterans. There were no significant differences between rural and urban Veterans in regards to age (72 vs 70), race (86% vs 87% White), pack years (37 vs 43), FEV1% predicted (58% vs 61%), educational attainment and employment status. There was no significant difference in health-related questions between rural and urban Veterans, CAT score (16.3 vs 14.9), PHQ-4 score (3 vs 2), PSS-4 score (10 vs 10), acute COPD exacerbation in the preceding 6 months (66% vs 56%), COVID vaccination rate (80% vs 80%), a history of COVID diagnosis (5.5% vs 12%) and consistent use of face masking (83% vs 91%). CONCLUSIONS We observed no significant differences in health status or mitigation practices between rural and urban Veterans during the COVID-19 pandemic. This includes no statistically significant difference of COVID 19 infection, vaccination rates, acute COPD exacerbation, PHQ-4 and PSS-4 scales.

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