GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

Eukaryotes in the gut microbiota in myalgic encephalomyelitis/chronic fatigue syndrome.

Mandarano AH[1], Giloteaux L[1], Keller BA[2], Levine SM[1], Hanson MR[1].

PeerJ. **2018 Jan 22**;6:e4282. doi: 10.7717/peerj.4282. PMCID: PMC5784577. eCollection 2018.

Patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) often suffer from gastrointestinal symptoms and many are diagnosed with irritable bowel syndrome (IBS). Previous studies, including from our laboratory, have demonstrated that the ME/CFS gut bacterial composition is altered and less diverse when compared to healthy individuals. Patients have increased biomarkers of inflammation and leaky gut syndrome. To further investigate dysbiosis in the ME/CFS gut microbiome, we sought to characterize the eukaryotes present in the gut of 49 individuals with ME/CFS and 39 healthy controls. Using 18S rRNA sequencing, we have identified eukaryotes in stool samples of 17 healthy individuals and 17 ME/CFS patients. Our analysis demonstrates a small, nonsignificant decrease in eukaryotic diversity in ME/CFS patients compared to healthy individuals. In addition, ME/CFS patients show a nonsignificant increase in the ratio of fungal phyla *Basidiomycota* to *Ascomycota*, which is consistent with ongoing inflammation in ME/CFS. We did not identify specific eukaryotic taxa that are associated with ME/CFS disease status.

Development and Validation of a Serologic Test Panel for Detection of Powassan Virus Infection in U.S. Patients Residing in Regions Where Lyme Disease Is Endemic.

Thomm AM[1], Schotthoefer AM[2], Dupuis AP 2nd[3], Kramer LD[3], Frost HM[4], Fritsche TR[4], Harrington YA[1], Knox KK[1], Kehl SC[5].

mSphere. **2018 Jan 10**;3(1). pii: e00467-17. doi: 10.1128/mSphere.00467-17. PMCID: PMC5760746. eCollection 2018 Jan-Feb.

Powassan virus (POWV) is an emerging tick-borne arbovirus presenting a public health threat in North America. POWV lineage II, also known as deer tick virus, is the strain of the virus most frequently found in *Ixodes scapularis* ticks and is implicated in most cases of POWV encephalitis in the United States. Currently, no commercial tests are available to detect POWV exposure in tick-borne disease (TBD) patients. We describe here the development and analytical validation of a serologic test panel to detect POWV infections. The panel uses an indirect enzyme immunoassay (EIA) to screen. EIA-positive samples reflex to a laboratory-developed, POWV-specific immunofluorescence assay (IFA). The analytical sensitivity of the test panel was 89%, and the limit of detection was a plaque reduction neutralization test (PRNT) titer of 1:20. The analytical specificity was 100% for the IgM assay and 65% for the IgG assay when heterologous-flavivirus-positive samples were tested. On samples collected from regions where Lyme disease is endemic, seroprevalence for POWV in TBD samples was 9.4% (10 of 106) versus 2% when tested with non-TBD samples (2 of 100, $P = 0.034$). No evidence of POWV infection was seen in samples collected from a region where Lyme disease was not endemic (0 of 22). This test panel provides a sensitive and specific platform for detecting a serologic response to POWV early in the course of infection when neutralizing antibodies may not be detectable. Combined with clinical history, the panel is an effective tool for identifying acute POWV infection.

IMPORTANCE: Approximately 100 cases of POWV disease were reported in the United States over the past 10 years. Most cases have occurred in the Northeast (52) and Great Lakes (45) regions (https://www.cdc.gov/powassan/statistics.html). The prevalence of POWV in ticks and mammals is increasing, and POWV poses an increasing threat in a greater geographical range. In areas of the Northeast and Midwest where Lyme disease is endemic, POWV testing is recommended for patients with a recent tick bite, patients with Lyme disease who have been treated with antibiotics, or patients with a tick exposure who have tested negative for Lyme disease or other tick-borne illnesses and have persistent symptoms consistent with posttreatment Lyme disease. Testing could also benefit patients with tick exposure and unexplained neurologic symptoms and chronic fatigue syndrome (CFS) patients with known tick exposure. Until now, diagnostic testing for Powassan virus has not been commercially available and has been limited to patients presenting with severe, neurologic complications. The lack of routine testing for Powassan virus in patients with suspected tick-borne disease means that little information is available regarding the overall prevalence of the virus and the full spectrum of clinical symptoms associated with infection. As *Ixodes scapularis* is the tick vector for Powassan virus and multiple other tick-borne pathogens, including the Lyme disease bacterium, *Borrelia burgdorferi*, the clinical presentations and long-term outcomes of Powassan virus infection and concurrent infection with other tick-borne disease pathogens remain unknown.

HEADACHE and MIGRAINE

Migraine with visual aura associated with thicker visual cortex.

Gaist D[1,2], Hougaard A[3], Garde E[4], Reislev NL[4], Wiwie R[5], Iversen P[4], Madsen CG[4,6], Blaabjerg M[1,2], Nielsen HH[1,2], Krøigård T[1,2], Østergaard K[1,2], Kyvik KO[2,7,8], Hjelmborg J[5], Madsen K[4], Siebner HR[4,9], Ashina M[3].

Brain. **2018 Jan 18**. doi: 10.1093/brain/awx382. [Epub ahead of print]

Until recent years it was believed that migraine with aura was a disorder causing intermittent neurological symptoms, with no impact on brain structure. However, recent MRI studies have reported increased cortical thickness of visual and somatosensory areas in patients with migraine with aura, suggesting that such structural alterations were either due to increased neuronal density in the areas involved, or a result of multiple episodes of cortical spreading depression as part of aura attacks. Subsequent studies have yielded conflicting results, possibly due to methodological reasons, e.g. small number of subjects. In this cross-sectional study, we recruited females aged 30-60 years from the nationwide Danish Twin Registry. Brain MRI of females with migraine with aura (patients), their co-twins, and unrelated migraine-free twins (controls) were performed at a single centre and assessed for cortical thickness in predefined cortical areas (V1, V2, V3A, MT, somatosensory cortex), blinded to headache diagnoses. The difference in cortical thickness between patients and controls adjusted for age, and other potential confounders was assessed. Comparisons of twin pairs discordant for migraine with aura were also performed. Comparisons were based on 166 patients, 30 co-twins, and 137 controls. Compared with controls, patients had a thicker cortex in areas V2 [adjusted mean difference 0.032 mm (95% confidence interval 0.003 to 0.061), V3A [adjusted mean difference 0.037 mm (95% confidence interval 0.008 to 0.067)], while differences in the remaining areas examined were not statistically significant [adjusted mean difference (95% confidence interval): V1 0.022 (-0.007 to 0.052); MT: 0.018 (-0.011 to 0.047); somatosensory cortex: 0.020 (-0.009 to 0.049)]. We found no association between the regions of interest and active migraine, or number of lifetime aura attacks. Migraine with aura discordant twin pairs (n = 30) only differed in mean thickness of V2 (0.039 mm, 95% CI 0.005 to 0.074). In conclusion, females with migraine with aura have a thicker cortex corresponding to visual areas and our results indicate this may be an inherent trait rather than a result of repeated aura attacks.

Genome-wide DNA methylation profiling in whole blood reveals epigenetic signatures associated with migraine.

Gerring ZF[1], McRae AF[2,3], Montgomery GW[2], Nyholt DR[4].

BMC Genomics. **2018 Jan 22**;19(1):69. doi: 10.1186/s12864-018-4450-2.

BACKGROUND: Migraine is a common heritable neurovascular disorder typically characterised by episodic attacks of severe pulsating headache and nausea, often accompanied by visual, auditory or other sensory symptoms. Although genome-wide association studies have identified over 40 single nucleotide polymorphisms associated with migraine, there remains uncertainty about the casual genes involved in disease pathogenesis and how their function is regulated.

RESULTS: We performed an epigenome-wide association study, quantifying genome-wide patterns of DNA methylation in 67 migraine cases and 67 controls with a matching age and sex distribution. Association analyses between migraine and methylation probe expression, after adjustment for cell type proportions, indicated an excess of small P values, but there was no significant single-probe association after correction for multiple testing ($P < 1.09 \times 10^{-7}$). However, utilising a 1 kb sliding window approach to combine adjacent migraine-methylation association P values, we identified 62 independent differentially methylated regions (DMRs) underlying migraine (false discovery rate < 0.05). Migraine association signals were subtle but consistent in effect direction across the length of each DMR. Subsequent analyses showed that the migraine-associated DMRs were enriched in regulatory elements of the genome and were in close proximity to genes involved in solute transportation and haemostasis.

CONCLUSIONS: This study represents the first genome-wide analysis of DNA methylation in migraine. We have identified DNA methylation in the whole blood of subjects associated with migraine, highlighting novel loci that provide insight into the biological pathways and mechanisms underlying migraine pathogenesis.

HEADACHE and MIGRAINE (Continued)

Changes in hormones of the hypothalamic-pituitary-gonadal axis in migraine patients.

Li W[1], Diao X[1], Chen C[2], Li C[1], Zhang Y[1], Li Y[1].

J Clin Neurosci. **2018 Jan 20**. pii: S0967-5868(17)30592-1. doi: 10.1016/j.jocn.2017.11.011. [Epub ahead of print]

The incidence of migraine is higher in women than in men. Abnormality of the hypothalamus-pituitary-gonadal (HPG) axis is believed to be implicated in the pathogenesis of migraine. The aim of this study was to detect serum hormone levels in the HPG axis of migraineurs and analyze the relationship between the hormone levels and migraine-related clinical characteristics. One hundred and nineteen migraineurs were enrolled. Serum FSH, LH, estradiol, progesterone, testosterone, prolactin and GnRH was detected. Pain intensity and migraine-related disability were evaluated using the visual analogue scale (VAS) and the Migraine Disability Assessment questionnaire (MIDAS). The relationships between sex hormone levels and the VAS score and the MIDAS score were also examined. Progesterone levels in male migraineurs were lower than those in healthy controls ($P < .01$). In female patients, in the follicular phase, testosterone levels were lower than in healthy controls ($P < .01$). In the luteal phase, estrogen and testosterone levels ($P < .05$) were lower than in healthy controls. Progesterone and testosterone levels ($P < .01$) were lower than in healthy controls in the postmenopausal phase. In male patients, estrogen levels were negatively associated with the MIDAS score ($r = -0.602$). In female patients, in the follicular phase, estrogen levels were positively correlated with headache duration and VAS score ($r = 0.374$, $r = 0.331$, respectively) and negatively related with MIDAS score ($r = -0.334$). In the luteal phase, estrogen and progesterone levels were negatively correlated with the MIDAS score ($r = -0.772$, $r = -0.464$, respectively). The levels of HPG axis hormones were abnormal in migraineurs and were associated with migraine-related clinical characteristics.

CHRONIC PAIN

Blockade of dopamine D2 receptors disrupts intrahippocampal connectivity and enhances pain-related working memory deficits in neuropathic pain rats.

Cardoso-Cruz H[1,2], Dourado M[1,2,3], Monteiro C[1,2], Galhardo V[1,2].

Eur J Pain. **2018 Jan 26**. doi: 10.1002/ejp.1186. [Epub ahead of print]

BACKGROUND: Dopamine (DA) is thought to be important to local hippocampal networks integrity during spatial working memory (sWM) processing. Chronic pain may contribute to deficient dopaminergic signalling, which may in turn affect cognition. However, the neural mechanisms that determine this impairment are poorly understood. Here, we evaluated whether the sWM impairment characteristic of animal models of chronic pain is dependent on DA D2 receptor (D2r) activity.

METHODS: To address this issue, we implanted multichannel arrays of electrodes in the dorsal and ventral hippocampal CA1 field (dvCA1) of rats and recorded the neuronal activity during a classical delayed food-reinforced T-maze sWM task. Within-subject behavioural performance and patterns of dorsoventral neural activity were assessed before and after the onset of persistent neuropathic pain using the spared nerve injury (SNI) model.

RESULTS: Our results show that the peripheral nerve lesion caused a disruption in sWM and hippocampus spike activity and that disruption was maximized by the systemic administration of the D2r antagonist raclopride. These deficits are strictly correlated with a selective disruption of hippocampal theta-oscillations. Particularly, we found a significant decrease in intrahippocampal CA1 field connectivity level.

CONCLUSIONS: Together, these results suggest that disruption of the dopaminergic balance in the intrahippocampal networks may be important for the development of cognitive deficits experienced during painful conditions.

SIGNIFICANCE: This study provides new insights into the role of D2r in the manifestation of pain-related sWM deficits. Our findings support that selective blockade of D2r produces a significant decrease in intrahippocampal connectivity mediated by theta-oscillations, and amplifies pain-related sWM deficits. These results suggest that further characterization of intrahippocampal dopaminergic modulation may be clinically relevant for the understanding of cognitive impairments that accompanies nociceptive stressful conditions.

CHRONIC PAIN (Continued)

Reporting of pain by people with chronic obstructive pulmonary disease (COPD): comparative results from the HUNT3 population-based survey.

Andenæs R[1], Momyr A[2], Brekke I[2].

BMC Public Health. **2018 Jan 25**;18(1):181. doi: 10.1186/s12889-018-5094-5.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is often associated with chronic pain, but pain in COPD remains poorly understood, particularly in comparison to pain in other groups. We compared the pain reported by people with COPD with that reported by arthritis, heart disease, diabetes, and those not reporting any disease, while adjusting for the effects of selected sociodemographic and lifestyle factors, comorbidities, anxiety, and depression.

METHODS: Using cross-sectional data from a population-based health survey in Norway (HUNT3; n = 50,807), we included participants with COPD (n = 1199), participants without COPD, but with arthritis (n = 8582), heart disease (n = 4109), or diabetes (n = 1254), and participants without any disease (n = 18,811). Logistic and linear regression analyses were performed to estimate the probability of reporting chronic pain and the level of pain intensity in the different groups adjusting for other relevant factors.

RESULTS: Approximately half (51.8%) of people with COPD reported chronic pain, which was a significantly higher rate than in the diabetes and non-disease groups, and similar to the heart disease group. People with arthritis had a chronic pain rate of 75.4%, which was higher than all other groups, including COPD. Analyses of pain intensity yielded similar findings, with the COPD group having higher pain intensity than the diabetes and non-disease groups, similar pain intensity as the heart disease group, and less pain intensity than the arthritis group. The likelihood of chronic pain and the intensity of pain were generally higher among women, people employed in occupations with low educational requirements, smokers, and those with comorbidity. Chronic pain rates and pain intensity increased with age and higher anxiety and depression scores, and were inversely related to physical activity.

CONCLUSIONS: People with COPD are at increased risk for chronic pain and higher pain intensity, second only to those with arthritis among the disease groups included in this study. The findings indicate a close relationship between pain and anxiety and depression. The relationships between pain and socioeconomic and lifestyle factors (e.g., smoking and exercise) suggest the need for efforts at the societal level to reduce inequality in health.

Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review [Internet].

Editors: Kansagara D, O'Neil M, Nugent S, Freeman M, Low A, Kondo K, Elven C, Zakher B, Motu'apuaka M, Paynter R, Morasco BJ.

Washington (DC): Department of Veterans Affairs (US); **2017 Aug**.

Link to full text in VA Evidence-based Synthesis Program Reports: *Prepared for:* Department of Veterans Affairs, Veterans Health Administration, Quality Enhancement Research Initiative, Health Services Research & Development Service, Washington, DC 20420. *Prepared by:* Evidence-based Synthesis Program (ESP), Portland VA Medical Center, Portland, OR, Devan Kansagara, MD, MCR, Director. This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the VA Portland Health Care System, Portland, OR, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative.

Excerpt: Eight states and the District of Columbia have legalized cannabis use for recreational purposes, and 28 states plus the District of Columbia have legalized cannabis for medical purposes. Recent studies suggest that 45-80% of individuals who seek cannabis for medical purposes do so for pain management, and an estimated 6%-39% of patients prescribed opioid medication for pain are also utilizing cannabis. Over one-third of patients seeking cannabis for medical purposes list post-traumatic stress disorder (PTSD) as the primary reason for the request. Approximately 15% of Veterans who are treated in Department of Veterans Affairs (VA) outpatient PTSD clinics report recent (past 6 months) cannabis use.

CHRONIC PAIN (Continued)

Self-system therapy for distress associated with persistent low back pain: A randomized clinical trial.

Waters SJ[1,2], Strauman TJ[3], McKee DC[1], Campbell LC [1,4], Shelby RA[1], Dixon KE[1,5,6], Fras AM[3], Keefe FJ[1].

Psychother Res. **2016 Jul**;26(4):472-83. doi: 10.1080/10503307.2015.1040485. PMCID: PMC4681700. Epub 2015 Jun 16.

OBJECTIVE: Persistent low back pain (PLBP) is associated with vulnerability to depression. PLBP frequently requires major changes in occupation and lifestyle, which can lead to a sense of failing to attain one's personal goals (self-discrepancy).

METHOD: We conducted a clinical trial to examine the efficacy of self-system therapy (SST), a brief structured therapy for depression based on self-discrepancy theory. A total of 101 patients with PLBP and clinically significant depressive symptoms were randomized either to SST, pain education, or standard care.

RESULTS: Patients receiving SST showed significantly greater improvement in depressive symptoms. Reduction in self-discrepancy predicted reduction in depressive symptoms only within the SST condition.

CONCLUSIONS: Findings support the utility of SST for individuals facing persistent pain and associated depression.

A qualitative analysis of patient-identified adaptive behaviour changes following interdisciplinary Acceptance and Commitment Therapy for chronic pain.

Thompson M[1], Vowles KE[2,3], Sowden G[3], Ashworth J[3], Levell J[3].

Eur J Pain. **2018 Jan 26**. doi: 10.1002/ejp.1184. [Epub ahead of print]

BACKGROUND: Interdisciplinary treatment programmes for chronic pain have strong evidence of treatment effect both immediately after treatment and at follow-up. However, despite strong outcome evidence, it is less clear which specific changes in behaviour are most relevant to patients or to outcomes. Indeed, it is not unknown for clinicians and patients to have different views with regard to goals of treatment. This study sought to evaluate the patients' perspective regarding important behavioural changes that occurred while they were enrolled in a 4-week interdisciplinary programme of Acceptance and Commitment Therapy (ACT) for chronic pain.

METHODS: Qualitative data were collected during a treatment session towards the end of treatment. In total, 104 completers from 16 consecutive treatment groups contributed to a data set consisting of 315 unique qualitative comments.

RESULTS: Thematic analysis resulted in a theme hierarchy including overarching themes, midlevel themes and subthemes. Three overarching themes were identified as follows: (1) interacting with self - describing an interplay between various aspects of the individual, (2) activity - concerning how individuals practically and sustainably undertook activities and (3) interacting with others - exploring relationships with other people. The results section further describes the midlevel and subthemes that cluster under the overarching themes.

CONCLUSIONS: These data provide initial insights into the patient's perspective of adaptive behavioural changes gained as part of an interdisciplinary programme of chronic pain rehabilitation. Overall, the data suggest the importance of a mix of both ACT-specific and more universal coping/pain rehabilitation elements. Future research may examine how these processes relate more directly to treatment outcome.

SIGNIFICANCE: This study provides new qualitative insights into the patient's perspective of adaptive behavioural changes gained as part of interdisciplinary pain rehabilitation. This and future work may help provide a more detailed understanding of the processes and behaviours that result in successful rehabilitation outcomes.

CHRONIC PAIN (Continued)

Gender Differences in Pain Experience and Treatment after Motor Vehicle Collisions: A Secondary Analysis of the CRASH Injury Study.

Madsen TE[1], McLean S[2], Zhai W[3], Linnstaedt S[4], Kurz MC[5], Swor R[6], Hendry P[7], Peak D[8], Lewandowski C[9], Pearson C[10], O'Neil B[10], Datner E[11], Lee D[12], Beaudoin F[13].

Clin Ther. **2018 Jan 19**. pii: S0149-2918(17)31120-7. doi: 10.1016/j.clinthera.2017.12.014. [Epub ahead of print]

PURPOSE: Little is known about gender differences in the treatment of pain after motor vehicle collisions (MVCs) in an emergency department (ED). We aimed to describe gender differences in pain experiences and treatment, specifically the use of opioids and benzodiazepines after ED discharge, for MVC-related pain.

METHODS: This was a secondary analysis of previously collected data from the CRASH Injury studies. We included patients who were seen and discharged from an ED after an MVC and who were enrolled in 1 of 2 multicenter longitudinal prospective cohort studies (1 black/non-Hispanic and 1 white/non-Hispanic). First, we compared the experience of pain as defined by self-reported moderate-to-severe axial pain, widespread pain, number of somatic symptoms, pain catastrophizing, and peritraumatic distress between women and men using bivariate analyses. We then determined whether there were gender differences in the receipt of prescription medications for post-MVC pain symptoms (opioids and benzodiazepines) using multivariate logistic regression adjusting for demographic characteristics, pain, and collision characteristics.

FINDINGS: In total, 1878 patients were included: 61.4% were women. More women reported severe symptoms on the pain catastrophizing scale (36.8% vs 31.0%; P = 0.032) and peritraumatic distress following the MVC (59.7% vs 42.5%; P < 0.001), and women reported more somatic symptoms than men (median, 3.9; interquartile range, 3.7-4.0 vs median, 3.3; interquartile range, 3.1-3.5; P < 0.001). Unadjusted, similar proportions of women and men were given opioids (29.2% vs 29.7%; P = 0.84). After adjusting for covariates, women and men remained equally likely to receive a prescription for opioids (relative risk = 0.83; 95% confidence interval, 0.58-1.19). Women were less likely than men to receive a benzodiazepine at discharge from an ED (relative risk = 0.53; 95% confidence interval, 0.32-0.88).

IMPLICATIONS: In a large, multicenter study of ED patients treated for MVC, there were gender differences in the acute psychological response to MVC with women reporting more psychological and somatic symptoms. Women and men were equally likely to receive opioid prescriptions at discharge. Future research should investigate potential gender-specific interventions to reduce both posttraumatic distress and the risk of developing negative long-term outcomes like chronic pain.

Systematic review: psychosocial factors associated with pain in inflammatory bowel disease.

Sweeney L[1], Moss-Morris R[2], Czuber-Dochan W[1], Meade L[3], Chumbley G[4], Norton C[1].

Aliment Pharmacol Ther. **2018 Jan 22**. doi: 10.1111/apt.14493. [Epub ahead of print]

BACKGROUND: Pain is a frequently reported symptom of inflammatory bowel disease (IBD) experienced by patients in active disease and remission. Psychological factors play a significant role in pain, but have not been systematically reviewed in IBD.

AIM: To review psychosocial factors associated with pain in adults diagnosed with IBD.

METHODS: Electronic (PsycInfo, MEDLINE, EMBASE, Cochrane Library, CINAHL, Web of Science), and hand-searching were conducted February-May 2017. Two authors carried out screening and data extraction.

RESULTS: Fifteen studies including 5539 IBD patients were identified. Emotional, cognitive-behavioural and personality factors were associated with IBD-pain. Depression and anxiety were the most commonly explored constructs, followed by perceived stress and pain catastrophising, all of which were positively associated with greater pain. Greater abdominal pain was associated with a concurrent mood disorder over fivefold (OR 5.76, 95% CI 1.39, 23.89). Coping strategies and pain fear avoidance correlated with pain levels. Perceived social support (r = .26) and internal locus of control (r = .33) correlated with less pain. Patients reporting pain in IBD remission more frequently had an existing diagnosis of a mood disorder, a chronic pain disorder and irritable bowel syndrome. Six studies controlled for disease activity, of which 4 found that psychosocial factors significantly predicted pain. The majority of studies (n = 10) were of high quality.

CONCLUSION: Psychosocial factors appear to play a significant role in IBD-pain. Further research is required to explore psychosocial constructs in relation to IBD-pain, with use of validated pain measures, large sample sizes and clearer characterisation of disease activity.

CHRONIC PAIN (Continued)

A randomized matched-pairs study of feasibility, acceptability, and effectiveness of systems consultation: a novel implementation strategy for adopting clinical guidelines for Opioid prescribing in primary care.

Quanbeck A[1,2], Brown RT[3], Zgierska AE[3], Jacobson N[4], Robinson JM[5], Johnson RA[3], Deyo BM[3], Madden L[6], Tuan WJ[3], Alagoz E[7].

Implement Sci. **2018 Jan 25**;13(1):21. doi: 10.1186/s13012-018-0713-1.

BACKGROUND: This paper reports on the feasibility, acceptability, and effectiveness of an innovative implementation strategy named "systems consultation" aimed at improving adherence to clinical guidelines for opioid prescribing in primary care. While clinical guidelines for opioid prescribing have been developed, they have not been widely implemented, even as opioid abuse reaches epidemic levels.

METHODS: We tested a blended implementation strategy consisting of several discrete implementation strategies, including audit and feedback, academic detailing, and external facilitation. The study compares four intervention clinics to four control clinics in a randomized matched-pairs design. Each systems consultant aided clinics on implementing the guidelines during a 6-month intervention consisting of monthly site visits and teleconferences/videoconferences. The mixed-methods evaluation employs the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework. Quantitative outcomes are compared using time series analysis. Qualitative methods included focus groups, structured interviews, and ethnographic field techniques.

RESULTS: Seven clinics were randomly approached to recruit four intervention clinics. Each clinic designated a project team consisting of six to eight staff members, each with at least one prescriber. Attendance at intervention meetings was 83%. More than 80% of staff respondents agreed or strongly agreed with the statements: "I am more familiar with guidelines for safe opioid prescribing" and "My clinic's workflow for opioid prescribing is easier." At 6 months, statistically significant improvements were noted in intervention clinics in the percentage of patients with mental health screens, treatment agreements, urine drug tests, and opioid-benzodiazepine co-prescribing. At 12 months, morphine-equivalent daily dose was significantly reduced in intervention clinics compared to controls. The cost to deliver the strategy was $7345 per clinic. Adaptations were required to make the strategy more acceptable for primary care. Qualitatively, intervention clinics reported that chronic pain was now treated using approaches similar to those employed for other chronic conditions, such as hypertension and diabetes.

CONCLUSIONS: The systems consultation implementation strategy demonstrated feasibility, acceptability, and effectiveness in a study involving eight primary care clinics. This multi-disciplinary strategy holds potential to mitigate the prevalence of opioid addiction and ultimately may help to improve implementation of clinical guidelines across healthcare.

TRIAL REGISTRATION: ClinicalTrials.gov (NCT02433496). https://clinicaltrials.gov/ct2/show/NCT02433496 Registered May 5, 2015.

OTHER RESEARCH OF INTEREST

Health Status of Gulf War and Era Veterans Serving in the US Military in 2000.

Porter B[1], Long K, Rull RP, Dursa EK; Millennium Cohort Study Team.

J Occup Environ Med. **2018 Jan 24**. doi: 10.1097/JOM.0000000000001280. PMID: 29370011. [Epub ahead of print]

OBJECTIVE: This research describes Gulf War and era veterans enrolled in the Millennium Cohort Study, who were sampled from US military personnel serving in 2000, and compares Health characteristics of this sample to a Department of Veterans' Affairs study sampled from the complete population.

METHODS: Demographics characteristics of this sample were described. Self-reported health characteristics were compared between the two studies.

RESULTS: Gulf War and era veterans in the Millennium Cohort were generally healthier than in the VA study; they had fewer medical conditions and mental health disorders and better self-reported health. In both studies, Gulf War veterans had poorer health outcomes than era veterans.

CONCLUSION: The Millennium Cohort Study is a unique resource for examining the long-term health effects of Gulf War deployment, particularly comparing deployed and nondeployed personnel and examining illnesses with long latencies.

OTHER RESEARCH OF INTEREST (Continued)

A Case Study of the NCRP 156 Wound Model of Embedded DU Using Data From Urine Uranium Concentrations of Wounded Veterans.

Walkingstick MT[1], Krage ES, Brey RR.

Health Phys. **2018 Mar**;114(3):373-378. doi: 10.1097/HP.0000000000000816. PMID: 29369940.

Depleted uranium (DU) munitions were initially used by the United States (U.S.) military during the first Persian Gulf War in 1991 in order to penetrate heavily armored vehicles. However, as a result of friendly fire, several U.S. military personnel received intakes from DU munitions. One of the ongoing concerns for these wounded veterans is the potential long-term exposure received from DU embedded fragments. The United States Army Institute of Public Health (AIPH) is the first laboratory that analyzes the urine bioassays from Army Soldiers that are injured with DU fragments. The United States Air Force School of Aerospace Medicine also evaluates bioassays from DU injuries. The urine bioassay data collected by AIPH was evaluated using the NCRP 156 wound model coefficients for the DU-Wafer, Fragment, and Particle models. The maximum likelihood method was used in the Integrated Modules for Bioassay Analysis (IMBA-PPAE) to calculate the estimates of intake and tissue doses. Evaluating the three models for wound retention, the DU-Wafer and Fragment model yielded a credible fit to the bioassay data. Comparing the two models, the DU-Wafer model fits the data better than the Fragment model when comparing their autocorrelation coefficient and chi-squared values of (P 1.73 × 10, c 4.83 × 10), (P 2.01 × 10, c 1.09), respectively. This evaluation supports the validity of both the DU-wafer model as well as the default fragmentation model proposed by NCRP 156.

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.

Kwong JC[1], Schwartz KL[1], Campitelli MA[1], Chung H[1], Crowcroft NS[1], Karnauchow T[1], Katz K[1], Ko DT[1], McGeer AJ[1], McNally D[1], Richardson DC[1], Rosella LC[1], Simor A[1], Smieja M[1], Zahariadis G[1], Gubbay JB[1].

N Engl J Med. **2018 Jan 25**;378(4):345-353. doi: 10.1056/NEJMoa1702090. PMID: 29365305.

BACKGROUND: Acute myocardial infarction can be triggered by acute respiratory infections. Previous studies have suggested an association between influenza and acute myocardial infarction, but those studies used nonspecific measures of influenza infection or study designs that were susceptible to bias. We evaluated the association between laboratory-confirmed influenza infection and acute myocardial infarction.

METHODS: We used the self-controlled case-series design to evaluate the association between laboratory-confirmed influenza infection and hospitalization for acute myocardial infarction. We used various high-specificity laboratory methods to confirm influenza infection in respiratory specimens, and we ascertained hospitalization for acute myocardial infarction from administrative data. We defined the "risk interval" as the first 7 days after respiratory specimen collection and the "control interval" as 1 year before and 1 year after the risk interval.

RESULTS: We identified 364 hospitalizations for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test result for influenza. Of these, 20 (20.0 admissions per week) occurred during the risk interval and 344 (3.3 admissions per week) occurred during the control interval. The incidence ratio of an admission for acute myocardial infarction during the risk interval as compared with the control interval was 6.05 (95% confidence interval [CI], 3.86 to 9.50). No increased incidence was observed after day 7. Incidence ratios for acute myocardial infarction within 7 days after detection of influenza B, influenza A, respiratory syncytial virus, and other viruses were 10.11 (95% CI, 4.37 to 23.38), 5.17 (95% CI, 3.02 to 8.84), 3.51 (95% CI, 1.11 to 11.12), and 2.77 (95% CI, 1.23 to 6.24), respectively.

CONCLUSIONS: We found a significant association between respiratory infections, especially influenza, and acute myocardial infarction. (Funded by the Canadian Institutes of Health Research and others.).

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