GULF WAR ILLNESS

1. Comparability of health service use by veterans with multisymptom **illness** and those with chronic diseases.

Gwini SM[1], Forbes AB[1], Sim MR[1], Kelsall HL[1]

Int J Qual Health Care. 2017 Jan 9. doi: 10.1093/intqhc/mzw140. [Epub ahead of print]

OBJECTIVE: To compare health service utilization and disability claims among military personnel with multisymptom illness (MSI) (but no chronic diseases), those with chronic disease(s) and those without MSI or chronic diseases. MSI is also known as Gulf War illness.

DESIGN: Cohort study. SETTING: Australia.

PARTICIPANTS: In total, 1288 participants of a Gulf War veterans' study conducted in 2000-2003 (Wave-1) were followed up in 2011-2012 (Wave-2), aged on average 40 years. About 160 had MSI, 217 had chronic disease(s) and 911 had neither chronic disease(s) nor MSI.

METHODS: At Wave-2, the cohort was linked to the national Medicare and Department of Veterans' Affairs (DVA) databases to obtain health service utilization and disability claims data recorded between 2001 and 2012.

RESULTS: The likelihood of visiting a general practitioner (GP) (risk ratio [RR] = 1.04, 95% confidence interval [CI] = 0.92, 1.19) or visiting a specialist medical doctor (RR = 0.83; 95% CI = 0.54, 1.28) or hospitalizations (RR = 0.89; 95% CI = 0.61, 1.29) or) in the 12 months preceding Wave-2 or successfully claiming for DVA disability compensation (RR = 1.13; 95% CI = 0.86, 1.47) was similar for personnel with MSI and those with chronic disease(s). However, GP consultations, hospitalizations, specialist doctor consultations and disability claims were significantly higher among those with MSI than those without MSI/chronic diseases.

CONCLUSIONS: Health service use and disability claims by personnel with MSI were comparable to those with chronic disease(s), but were in excess of those without MSI/chronic diseases. Hence recognition of the high health service use by personnel with MSI is important to ensure adequate provision of health services.

CHRONIC FATIGUE SYNDROME

1. A systematic review of the association between fatigue and genetic polymorphisms.

Wang T, Yin J, Miller AH, Xiao C.

Brain Behav Immun. 2017 Jan 12. pii: S0889-1591(17)30007-7. doi: 10.1016/j.bbi.2017.01.007. [Epub ahead of print] Review.

Fatigue is one of the most common and distressing symptoms, leading to markedly decreased quality of life among a large subset of patients with a variety of disorders. Susceptibility to fatigue may be influenced by genetic factors including single nucleotide polymorphisms (SNPs), especially in the regulatory regions, of relevant genes. To further investigate the association of SNPs with fatigue in various patient populations, a systematic search was conducted on Pubmed, CINAHL, PsycINFO, and Sociological Abstracts Database for fatigue related-terms in combination with polymorphisms or genetic variation-related terms. Fifty papers in total met the inclusion and exclusion criteria for this analysis. These 50 papers were further classified into three subgroups for evaluation: chronic fatigue syndrome (CFS), cancer-related fatigue (CRF) and other disease-related fatigue. SNPs in regulatory pathways of immune and neurotransmitter systems were found to play important roles in the etiologies of CFS, CRF and other disease-related fatigue. Evidence for associations between elevated fatigue and specific polymorphisms in TNFα, IL1b, IL4 and IL6 genes was revealed for all three subgroups of fatigue. We also found CFS shared a series of polymorphisms in HLA, IFN-γ, 5-HT and NR3C1 genes with other disease-related fatigue, however these SNPs (excluding IFN-γ) were not found to be adequately investigated in CRF. Gaps in knowledge related to fatigue etiology and recommendations for future research are further discussed.

CHRONIC FATIGUE SYNDROME (Continued)

2. Mortality in Patients with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome.

McManimen SL, Devendorf AR, Brown AA, Moore BC, Moore JH, Jason LA.

Fatigue. 2016;4(4):195-207. doi: 10.1080/21641846.2016.1236588.

BACKGROUND: There is a dearth of research examining mortality in individuals with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). Some studies suggest there is an elevated risk of suicide and earlier mortality compared to national norms. However, findings are inconsistent as other researchers have not found significant increases in all-cause mortality for patients.

OBJECTIVE: This study sought to determine if patients with ME or CFS are reportedly dying earlier than the overall population from the same cause.

METHODS: Family, friends, and caregivers of deceased individuals with ME or CFS were recruited through social media, patient newsletters, emails, and advocate websites. This study analyzed data including cause and age of death for 56 individuals identified as having ME or CFS.

RESULTS: The findings suggest patients in this sample are at a significantly increased risk of earlier all-cause (*M* = 55.9 years) and cardiovascular-related (*M* = 58.8 years) mortality, and they had a directionally lower mean age of death for suicide (*M* = 41.3 years) and cancer (*M* =66.3 years) compared to the overall U.S. population [*M* = 73.5 (all-cause), 77.7 (cardiovascular), 47.4 (suicide), and 71.1 (cancer) years of age].

CONCLUSIONS: The results suggest there is an increase in risk for earlier mortality in patients with ME and CFS. Due to the small sample size and over-representation of severely ill patients, the findings should be replicated to determine if the directional differences for suicide and cancer mortality are significantly different from the overall U.S. population.

HEADACHE MIGRAINE

1. Investigation of polymorphisms in genes involved in estrogen metabolism in menstruamigraine.

Sutherland HG, Champion M, Plays A, Stuart S, Haupt LM, Frith A, Anne MacGregor E, Griffiths LR.

Gene. 2017 Jan 13. pii: S0378-1119(17)30019-7. doi: 10.1016/j.gene.2017.01.008. [Epub ahead of print]

Migraine is a common, disabling headache disorder, which is influenced by multiple genes and environmental triggers. After puberty, the prevalence of migraine in women is three times higher than in men and >50% of females suffering from migraine report a menstrual association, suggesting hormonal fluctuations can influence the risk of migraine attacks. It has been hypothesized that the drop in estrogen during menses is an important trigger for menstrual migraine. Catechol-O-methyltransferase (COMT) and Cytochrome P450 (CYP) enzymes are involved in estrogen synthesis and metabolism. Functional polymorphisms in these genes can influence estrogen levels and therefore may be associated with risk of menstrual migraine. In this study we investigated four single nucleotide polymorphisms in three genes involved in estrogen metabolism that have been reported to impact enzyme levels or function, in a specific menstrual migraine cohort. 268 menstrual migraine cases and 142 controls were genotyped for rs4680 in COMT (Val158Met), rs4646903 and rs1048943 in CYP1A1 (T3801C and Ile462Val) and rs700519 in CYP19A1 (Cys264Arg). Neither genotype nor allele frequencies for the COMT and CYP SNPs genotyped were found to be significantly different between menstrual migraineurs and controls by chi-square analysis (P>0.05). Therefore we did not find association of functional polymorphisms in the estrogen metabolism genes COMT, CYP1A1 or CYP19A1 with menstrual migraine. Further studies are required to assess whether menstrual migraine is genetically distinct from the common migraine subtypes and identify genes that influence risk.

HEADACHE MIGRAINE (Continued)

2. Vestibular Migraine: Clinical Challenges and Opportunities for Multidisciplinarity.

Luzeiro I, Luís L, Gonçalves F, Pavão Martins I.

Behav Neurol. 2016;2016:6179805. doi: 10.1155/2016/6179805. Review.

Migraine and vertigo are two very prevalent conditions in general population. The coexistence of both in the same subject is a significant clinical challenge, since it is not always possible to understand whether they are causally related or associated by chance, requiring different diagnostic and therapeutic approaches. In this review we analyze and summarize the actual knowledge about vestibular migraine (VM), focusing on the new concepts proposed by the International Classification of Headache Disorders 3-beta and by the Bárány Society and also addressing the former concepts, which are still present in clinical practice. We conclude that clinical studies using a multidisciplinary approach are crucial in this field, since different specialists observe the same pathology with different eyes. Clinical presentation of VM is variable in what concerns vestibular symptoms temporal relation with migraine headache, as well as in their accompanying manifestations. Biomarkers, either genomics or functional, and molecular imaging techniques will be helpful to clarify many aspects of the complexity of this entity, helping to define to what extent can VM be considered a separate and independent clinical entity.

3. Lasmiditan for the treatment of migraine.

Capi M, de Andrés F, Lionetto L, Gentile G, Cipolla F, Borro M, Martelletti P, Curto M.

Expert Opin Investig Drugs. 2017 Jan 11. doi: 10.1080/13543784.2017.1280457. [Epub ahead of print]

Migraine is one of the most common diseases in the world, with high economical and subjective burden. Migraine acute therapy is nowadays based on specific and non-specific drugs but up to 40% of episodic migraineurs still have unmet treatment needs and over 35% do not benefit from triptans administration. Serotonin-1F receptors have been identified in trigeminal system and became an ideal target for anti-migraine drug development as potential trigeminal neural inhibitors. Lasmiditan, a novel serotonin1F receptor agonist, showed specific affinity in vitro for the receptor with any vasoconstrictive action and inhibited markers associated with electrical stimulation of trigeminal ganglion in migraine animal models. Areas covered: This article reviews both preclinical and clinical studies on lasmiditan as a potential acute therapy for migraine, as well as pharmacokinetic and pharmacodynamic features. It also summarizes safety and tolerability data gathered in the various human studies. Expert opinion: The absence of vasoconstrictive effects makes lasmiditan a promising novel migraine acute therapy. Although preclinical and Phase I and II studies established a significant efficacy, the limited knowledge about pharmacokinetics and metabolism, the high rate of non-serious central nervous system side effects and the lack of larger studies remain still a matter of concern that should be addressed in future studies.

HEADACHE MIGRAINE (Continued)

4. Occipital Nerve Stimulation for Refractory Chronic Migraine: Results of a Long-Term Prospective Study.

   Rodrigo D, Acin P, Bermejo P.

   Pain Physician. 2017 Jan-Feb;20(1):E151-E159.

BACKGROUND: Refractory chronic migraine affects approximately 4% of the population worldwide and results in severe pain, lifestyle limitations, and decreased quality of life. Occipital nerve stimulation (ONS) refers to the electric stimulation of the distal branches of greater and lesser occipital nerves; the surgical technique has previously been described and has demonstrated efficacy in the treatment of a wide variety of headache disorders.

OBJECTIVES: The aim of this study is to evaluate the long-term efficacy and tolerability of ONS for medically intractable chronic migraine.

STUDY DESIGN: Prospective, long-term, open-label, uncontrolled observational study.

SETTING: Single public university hospital.

METHODS: Patients who met the International Headache Society criteria for chronic migraine, all of them having been previously treated with other therapeutic alternatives, and who met all inclusion and exclusion criteria for neurostimulation, received the implantation of an ONS system after a positive psychological evaluation and a positive response to a preliminary occipital nerve blockage. The implantation was performed in 2 phases: a 10 day trial with implanted occipital leads connected to an external stimulator and, if more than 50% pain relief was obtained, permanent pulse generator implantation and connection to the previously implanted leads. After the surgery, the patients were thoroughly evaluated annually using different scales: pain Visual Analogue Scale (VAS), number of migraine attacks per month, sleep quality, functionality in social and labor activities, reduction in pain medication, patient satisfaction, tolerability, and reasons for termination. The average follow-up time was 9.4 ± 6.1 years, and 31 patients completed a 7-year follow-up period.

RESULTS: Thirty-seven patients were enrolled and classified according to the location and quality of their pain, accompanying symptoms, work status, and psychological effects. Substantial pain reduction was obtained in most patients, and the VAS decreased by 4.9 ± 2.0 points. These results remained stable over the follow-up period. Five of the 35 permanently implanted patients with migraine attacks at baseline were free from these attacks at their last visits, whereas the pain severity decreased 3.8 ± 2.5 (according to the VAS) in the remaining patients. Seven of the 35 permanent implanted devices were definitively removed: 2 devices because of treatment inefficacy, and 5 devices because the patients were asymptomatic and considered to be cured from their pain, even with the stimulation off. Systemic side effects were not observed.

LIMITATIONS: Limitations of the current study include its uncontrolled and open-label design. Additionally, not all patients completed the 7-year follow-up period.

CONCLUSIONS: We consider that the trigemino-cervical autonomous and cervical connection may explain why ONS might relieve chronic migraine pain, but this is just a theoretical explanation which should be demonstrated in future studies. The results achieved in this study suggest that ONS may provide long-term benefits for patients with medically intractable chronic migraine. These outcomes are slightly better than previous reports and were maintained over the 7-year follow-up. We believe that an accurate selection of patients, realization of diagnostic occipital nerve blocks, psychological evaluations, rigorous surgical technique, and appropriate parameter programming helped us achieve these outcomes.
Key words: Refractory chronic migraine, headache, occipital nerve stimulatino, peripheral nerve stimulation, occipital nerve block.

CHRONIC PAIN

1. Loss of μ opioid receptor signaling in nociceptors, but not microglia, abrogates morphine tolerance without disrupting analgesia.

   Corder G, Tawfik VL, Wang D, Sypek EI, Low SA, Dickinson JR, Sotoudeh C, Clark JD, Barres BA, Bohlen CJ, Scherrer G.

   Nat Med. 2017 Jan 16. doi: 10.1038/nm.4262. [Epub ahead of print]

Opioid pain medications have detrimental side effects including analgesic tolerance and opioid-induced hyperalgesia (OIH). Tolerance and OIH counteract opioid analgesia and drive dose escalation. The cell types and receptors on which opioids act to initiate these maladaptive processes remain disputed, which has prevented the development of therapies to maximize and sustain opioid analgesic efficacy. We found that μ opioid receptors (MORs) expressed by primary afferent nociceptors initiate tolerance and OIH development. RNA sequencing and histological analysis revealed that MORs are expressed by nociceptors, but not by spinal microglia. Deletion of MORs specifically in nociceptors eliminated morphine tolerance, OIH and pronociceptive synaptic long-term potentiation without altering antinociception. Furthermore, we found that co-administration of methylnaltrexone bromide, a peripherally restricted MOR antagonist, was sufficient to abrogate morphine tolerance and OIH without diminishing antinociception in perioperative and chronic pain models. Collectively, our data support the idea that opioid agonists can be combined with peripheral MOR antagonists to limit analgesic tolerance and OIH.

2. Long-lasting antinociceptive effects of green light in acute and chronic pain in rats.

   Ibrahim MM, Patwardhan A, Gilbraith KB, Moutal A, Yang X, Chew LA, Largent-Milnes T, Malan TP, Vanderah TW, Porreca F, Khanna R.

   Pain. 2017 Feb;158(2):347-360. doi: 10.1097/j.pain.0000000000000767.

Treatments for chronic pain are inadequate, and new options are needed. Nonpharmaceutical approaches are especially attractive with many potential advantages including safety. Light therapy has been suggested to be beneficial in certain medical conditions such as depression, but this approach remains to be explored for modulation of pain. We investigated the effects of light-emitting diodes (LEDs), in the visible spectrum, on acute sensory thresholds in naive rats as well as in experimental neuropathic pain. Rats receiving green LED light (wavelength 525 nm, 8 h/d) showed significantly increased paw withdrawal latency to a noxious thermal stimulus; this antinociceptive effect persisted for 4 days after termination of last exposure without development of tolerance. No apparent side effects were noted and motor performance was not impaired. Despite LED exposure, opaque contact lenses prevented antinociception. Rats fitted with green contact lenses exposed to room light exhibited antinociception arguing for a role of the visual system. Antinociception was not due to stress/anxiety but likely due to increased enkephalins expression in the spinal cord. Naloxone reversed the antinociception, suggesting involvement of central opioid circuits. Rostral ventromedial medulla inactivation prevented expression of light-induced antinociception suggesting engagement of descending inhibition. Green LED exposure also reversed thermal and mechanical hyperalgesia in rats with spinal nerve ligation. Pharmacological and proteomic profiling of dorsal root ganglion neurons from green LED-exposed rats identified changes in calcium channel activity, including a decrease in the N-type (CaV2.2) channel, a primary analgesic target. Thus, green LED therapy may represent a novel, nonpharmacological approach for managing pain.

CHRONIC PAIN (Continued)

3. Sociodemographic disparities in chronic pain, based on 12-year longitudinal data.

   Grol-Prokopczyk H.

   Pain. 2017 Feb;158(2):313-322. doi: 10.1097/j.pain.0000000000000762.

Existing estimates of sociodemographic disparities in chronic pain in the United States are based on cross-sectional data, often treat pain as a binary construct, and rarely test for nonresponse or other types of bias. This study uses 7 biennial waves of national data from the Health and Retirement Study (1998-2010; n = 19,776) to describe long-term pain disparities among older (age 51+) American adults. It also investigates whether pain severity, reporting heterogeneity, survey nonresponse, and/or mortality selection might bias estimates of social disparities in pain. In the process, the article clarifies whether 2 unexpected patterns observed cross-sectionally-plateauing of pain above age 60, and lower pain among racial/ethnic minorities-are genuine or artefactual. Findings show high prevalence of chronic pain: 27.3% at baseline, increasing to 36.6% thereafter. Multivariate latent growth curve models reveal extremely large disparities in pain by sex, education, and wealth, which manifest primarily as differences in intercept. Net of these variables, there is no racial/ethnic minority disadvantage in pain scores, and indeed a black advantage vis-à-vis whites. Pain levels are predictive of subsequent death, even a decade in the future. No evidence of pain-related survey attrition is found, but surveys not accounting for pain severity and reporting heterogeneity are likely to underestimate socioeconomic disparities in pain. The lack of minority disadvantage (net of socioeconomic status) appears genuine. However, the age-related plateauing of pain observed cross-sectionally is not replicated longitudinally, and seems partially attributable to mortality selection, as well as to rising pain levels by birth cohort.

4. New-onset depression following stable, slow, and rapid rate of prescription opioid dose escalation.

   Salas J, Scherrer JF, Schneider FD, Sullivan MD, Bucholz KK, Burroughs T, Copeland LA, Ahmedani BK, Lustman PJ.

   Pain. 2017 Feb;158(2):306-312. doi: 10.1097/j.pain.0000000000000763.

Recent studies suggest that longer durations of opioid use, independent of maximum morphine equivalent dose (MED) achieved, is associated with increased risk of new-onset depression (NOD). Conversely, other studies, not accounting for duration, found that higher MED increased probability of depressive symptoms. To determine whether rate of MED increase is associated with NOD, a retrospective cohort analysis of Veterans Health Administration data (2000-2012) was conducted. Eligible patients were new, chronic (>90 days) opioid users, aged 18 to 80, and without depression diagnoses for 2 years before start of follow-up (n = 7051). Mixed regression models of MED across follow-up defined 4 rate of dose change categories: stable, decrease, slow increase, and rapid increase. Cox proportional hazard models assessed the relationship of rate of dose change and NOD, controlling for pain, duration of use, maximum MED, and other confounders using inverse probability of treatment-weighted propensity scores. Incidence rate for NOD was 14.1/1000PY (person-years) in stable rate, 13.0/1000PY in decreasing, 19.3/1000PY in slow increasing, and 27.5/1000PY in rapid increasing dose. Compared with stable rate, risk of NOD increased incrementally for slow (hazard ratio = 1.22; 95% confidence interval: 1.05-1.42) and rapid (hazard ratio = 1.58; 95% confidence interval: 1.30-1.93) rate of dose increase. Faster rates of MED escalation contribute to NOD, independent of maximum dose, pain, and total opioid duration. Dose escalation may be a proxy for loss of control or undetected abuse known to be associated with depression. Clinicians should avoid rapid dose increase when possible and discuss risk of depression with patients if dose increase is warranted for pain.

CHRONIC PAIN (Continued)

5. Dietary intake mediates the relationship of body fat to pain.

   Emery CF, Olson KL, Bodine A, Lee V, Habash DL.

   Pain. 2017 Feb;158(2):273-277. doi: 10.1097/j.pain.0000000000000754.

Prior studies have documented an association of obesity with chronic pain, but the mechanism explaining the association remains unknown. This study evaluated the degree to which dietary intake of foods with anti-inflammatory effects mediates the relationship of body fat to body pain. Ninety-eight community-residing healthy adults (60% women; mean age = 43.2 ± 15.3 years; range: 20-78 years) participated in a home-based study of home environment, food-related behaviors, health, and adiposity. During a 3-hour home visit evaluation, 3 measures of body fat were collected, including height and weight for calculation of body mass index (BMI). Participants also completed a 24-hour food recall interview and self-report measures of bodily pain (BP; BP subscale from the Medical Outcomes Study Short Form-36) and psychological distress (Hospital Anxiety and Depression Scale). Quality of dietary intake was rated using the Healthy Eating Index-2010. Mediation models were conducted with the PROCESS macro in SAS 9.3. Mean BMI was consistent with obesity (30.4 ± 7.8; range: 18.2-53.3), and BP values (73.2 ± 22.1; range: 0-100) and dietary intake quality (59.4 ± 15.5; range: 26.8-88.1) were consistent with population norms. Modeling in PROCESS revealed that Healthy Eating Index-2010 scores mediated the relationship between BMI and BP (bindirect = -0.34, 95% confidence interval = -0.68 to -0.13). The mediation model remained significant when controlling for biomechanical factors (arthritis/joint pain), medication use, psychological distress, age, and education, and models remained significant using the other 2 body fat measures. Thus, the data indicate that dietary intake of foods with anti-inflammatory effects mediates the relationship of body fat to body pain in healthy men and women.

6. Long-term use of opioids for nonmalignant pain among community-dwelling persons with and without Alzheimer disease in Finland: a nationwide register-based study.

   Hamina A, Taipale H, Tanskanen A, Tolppanen AM, Karttunen N, Pylkkänen L, Tiihonen J, Hartikainen S.

   Pain. 2017 Feb;158(2):252-260. doi: 10.1097/j.pain.0000000000000752.

Persons with Alzheimer disease (AD) commonly present with chronic nonmalignant pain, but long-term use of opioids among this population has not been studied previously. Our aim was to investigate the prevalence of long-term (≥180 days) use of opioids for nonmalignant pain and associated factors among community-dwelling persons with AD and to compare the prevalence with a matched cohort without AD. The Medication use and Alzheimer's disease (MEDALZ) cohort was used for this study, comprising all community-dwelling persons diagnosed with AD in Finland during 2005 to 2011 and their matched comparison persons without AD. After exclusion of persons with active cancer treatment, 62,074 persons with and 62,074 persons without AD were included in this study. Data were collected from nationwide registers. Opioids were used by 13,111 persons with and by 16,659 without AD. Overall long-term opioid use was more common among persons without AD (8.7%) than among persons with AD (7.2%, P < 0.0001). However, among opioid users, prevalence of long-term opioid use was slightly higher among persons with AD than among those without AD (34.2% vs 32.3%, respectively, P = 0.0004). Long-term use of transdermal opioids was more than 2-fold among opioid users with AD (13.2%) compared with users without AD (5.5%). Factors associated with long-term opioid use included AD, age ≥80 years, female sex, rheumatoid arthritis, osteoporosis, low socioeconomic position, history of substance abuse, and long-term benzodiazepine use. Prevalence of long-term opioid use was somewhat similar among both groups. Among persons with AD, long-term opioid use was strongly associated with transdermal opioids.

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