GULF WAR ILLNESS

Exploring Brain Mechanisms Underlying Gulf War Illness with Group ICA based Analysis of fMRI Resting State Networks.

Gopinath KS[1], Sakoglu U[2], Crosson BA[3], Haley RW[4].

Neurosci Lett. **2019 Feb 27**. pii: S0304-3940(19)30141-7. doi: 10.1016/j.neulet.2019.02.041. [Epub ahead of print]

Around 200,000 veterans (up to 32% of those deployed) of the 1991 Gulf War (GW) suffer from GW illness (GWI), which is characterized by multiple deficits in cognitive, affective, sensory and nociception domains. In this study we employed resting state fMRI (rsfMRI) to map impairments in brain function in GWI with advanced network analysis. RsfMRI data was obtained from 60 GWI veterans and 30 age-matched military controls. Group independent component analysis (GICA) was conducted to probe the functional connectivity networks in all 90 subjects. GICA revealed impaired functional connectivity (FC) in GWI veterans between a number of brain function networks consistent with their self-reported symptoms. GWI veterans exhibited impaired FC between language networks, and sensory input networks of all modalities as well as motor output networks. GWI veterans also exhibited impaired FC between different sensory perception and motor networks, and between different networks in the sensorimotor domain. These FC impairments provide putative mechanism of central nervous system dysfunction in GWI.

CHRONIC FATIGUE SYNDROME

MtDNA population variation in Myalgic encephalomyelitis/Chronic fatigue syndrome in two populations: a study of mildly deleterious variants.

Venter M[1], Tomas C[2], Pienaar IS[3,4], Strassheim V [2,4], Erasmus E[1], Ng WF[2,5], Howell N[6], Newton JL[4,5], Van der Westhuizen FH[1], Elson JL[7,8].

Sci Rep. **2019 Feb 27**;9(1):2914. doi: 10.1038/s41598-019-39060-1. PMCID: PMC6393470. PMID: 30814539.

Myalgic Encephalomyelitis (ME), also known as Chronic Fatigue Syndrome (CFS) is a debilitating condition. There is growing interest in a possible etiologic or pathogenic role of mitochondrial dysfunction and mitochondrial DNA (mtDNA) variation in ME/CFS. Supporting such a link, fatigue is common and often severe in patients with mitochondrial disease. We investigate the role of mtDNA variation in ME/CFS. No proven pathogenic mtDNA mutations were found. We then investigated population variation. Two cohorts were analysed, one from the UK (n = 89 moderately affected; 29 severely affected) and the other from South Africa (n = 143 moderately affected). For both cohorts, ME/CFS patients had an excess of individuals without a mildly deleterious population variant. The differences in population variation might reflect a mechanism important to the pathophysiology of ME/CFS.

HEADACHE and MIGRAINE

Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition.

Diener HC[1], Tassorelli C[2,3], Dodick DW[4], Silberstein SD[5], Lipton RB[6], Ashina M[7], Becker WJ[8,9], Ferrari MD[10], Goadsby PJ[11], Pozo-Rosich P[12], Wang SJ[13,14], Mandrekar J[15]; International Headache Society Clinical Trials Standing Committee.

Cephalalgia. **2019 Feb 26**:333102419828967. doi: 10.1177/0333102419828967. PMID: 30806518. [Epub ahead of print]

The quality of clinical trials is an essential part of the evidence base for the treatment of headache disorders. In 1991, the International Headache Society Clinical Trials Standing Committee developed and published the first edition of the Guidelines for controlled trials of drugs in migraine. Scientific and clinical developments in headache medicine led to second and third editions in 2000 and 2012, respectively. The current, fourth edition of the Guidelines retains the structure and much content from previous editions. However, it also incorporates evidence from clinical trials published after the third edition as well as feedback from meetings with regulators, pharmaceutical and device manufacturers, and patient associations. Its final form reflects the collective expertise and judgement of the Committee. These updated recommendations and commentary are intended to meet the Society's continuing objective of providing a contemporary, standardized, and evidence-based approach to the conduct and reporting of randomised controlled trials for the acute treatment of migraine attacks.

HEADACHE and MIGRAINE (Continued)

Living with Migraine in Canada - A National Community-Based Study.

Altura KC[1], Patten SB[2], Williams JVA[2], Fiest KM[2], Jetté N[1].

Can J Neurol Sci. **2019 Feb 28**:1-8. doi: 10.1017/cjn.2019.3. PMID: 30816083. [Epub ahead of print]

OBJECTIVE: To develop a detailed profile of individuals living with migraine in Canada. Such a profile is important for planning and administration of services.

METHODS: The 2011-2012 Survey of Living with Neurological Conditions in Canada (SLNCC), a cross-sectional community-based survey, was used to examine a representative sample of migraineurs (N = 949) aged 15 years and older. Several health-related variables were examined (e.g., general health, health utility index (HUI) [a measure of health status and health-related quality of life, where dead = 0.00 and perfect health = 1.00], stigma, depression, and social support). Respondents were further stratified by sex, age, and age of migraine onset. Weighted overall and stratified prevalence estimates and odds ratios, both with 95% CIs, were used to estimate associations.

RESULTS: Overall, males had poorer health status compared with females (e.g., mean HUI was 0.67 in males vs. 0.82 in females; men had over two times the odds of their migraine limiting educational and job opportunities compared with females). Poorer health-related variables were seen in the older age groups (35-64 years/≥65 years) compared with the 15-34-year age group. There were no differences between those whose migraine symptoms began before versus after the age of 20 years.

CONCLUSIONS: In this Canadian sample, migraine was associated with worse health-related variables in men compared with women. However, both men and women were significantly affected by migraine across various health-related variables. Thus, it is important to improve clinical and public health interventions addressing the impact of migraine across individuals of all ages, sexes, and sociodemographic backgrounds.

A randomized trial of trigger point dry needling versus sham needling for chronic tension-type headache.

Gildir S[1], Tüzün EH[1], Eroğlu G[2], Eker L[1].

Medicine (Baltimore). **2019 Feb**;98(8):e14520. doi: 10.1097/MD.0000000000014520. PMID: 30813155.

BACKGROUND: In this randomized, double-blind, parallel-group trial, we aimed to explore the effectiveness of trigger point dry needling in patients with chronic tension-type headache in reducing headache frequency, intensity and duration, and improvement of health-related quality of life.

METHODS: The 168 patients in 2 neurology clinics with chronic tension-type headache. The participants were randomly assigned to one of two treatment groups for dry needling or sham dry needling, delivered in 3 sessions a week for 2 weeks. The 160 patients fulfilled the study requirements. The dry needling was applied in active trigger points located in the musculature of the head and the neck. The patients received dry needling using sterile stainless-steel acupuncture needles of 0.25×40mm and 0.25×25mm dimensions. The sham dry needling procedure was applied into the adipose tissue located at any area where an active trigger point was absent. The primary outcome measurement was the headache intensity. Secondary outcomes were frequency and duration of headache, and quality of life, assessed by the Short Form-36. All outcomes were measured at baseline, at the end of 2-week, and 1-month follow-up period.

RESULTS: In the dry needling group, intensity, frequency and duration of headache, and the scores of Short Form-36 subscales were significantly improved after treatment ($P < .05$). In the dry needling group, all the effect sizes for headache variables were large.

CONCLUSIONS: The results of this clinical trial suggest that trigger point dry needling in patients with chronic tension-type headache is effective and safe in reducing headache intensity, frequency and duration, and increasing health-related quality of life.

TRIAL REGISTRATION: Clinical Trials NCT03500861.

HEADACHE and MIGRAINE (Continued)

Sino-Nasal Anatomical Variations in Rhinogenic Headache Pathogenesis: A Case-Control Clinical Study.

Sollini G[1], Mazzola F, Iandelli A, Carobbio A, Barbieri A, Mora R, Peretti G.

J Craniofac Surg. **2019 Feb 20**. doi: 10.1097/SCS.0000000000005239. PMID: 30817544. [Epub ahead of print]

Rhinogenic headache (RH) is a widespread pain syndrome but its pathogenesis and treatment are still unclear. Some authors recognize a correlation between RH and mucosal contact points or some other sinonasal anatomical variations. The authors conducted a retrospective case-control study to analyze the correlation between radiological findings and clinical symptoms. One hundred-nineteen adults with Para-Nasal Sinuses Computed Tomography (PNS-CT) scans were included: 64 patients who have originally undergone PNS-CT scan as part of rhinogenic headache workup (Group A), and 55 controls in whom PNS-CT scans were obtained for other purposes (Group B). All subjects were asked to report their symptoms using a headache scoring system. PNS-CT scans of all subjects were analyzed for presence of mucosal contact points, middle turbinate concha bullosa (MTCB) and frontoethmoidal cells. The most common anatomical abnormality found in our series was MTCB, reported in 60.9% of patients in Group A and 41.8% of those in Group B. A statistically significant prevalence was found in Group A compared to Group B regarding the presence of MTCB (P=0.037) and Type II (P=0.016) and Type III (P=0.039) frontoethmoidal cells. No statistically significant difference (P>0.05) was found between Group A and Group B regarding the presence of mucosal contact points at each site. Multiple anatomical variations in nasal and paranasal sinuses may cause a rhinogenic headache with different characteristics. Some of these, such as concha bullosa of middle turbinate or type II and III Kuhn cells, have shown a significant association with rhinogenic headache. No statistically significant association was found between presence of headache and mucosal contact points and type I and IV frontal cells. These findings can be very helpful for the surgeons that want to deal with the treatment of RH.

Symptoms in cervical vertigo.

Thompson-Harvey A[1,2], Hain TC[2,3].

Laryngoscope Investig Otolaryngol. **2018 Nov 28**;4(1):109-115. doi: 10.1002/lio2.227. PMCID: PMC6383310. PMID: 30828627. eCollection 2019 Feb.

Objective: To use a unique, 41-question survey to identify patient features distinguishing cervical vertigo from vestibular causes of vertigo and vestibular migraine.

Methods: In this study, a unique, 41-question survey was administered to 48 patients diagnosed with cervical vertigo (n = 16), migraine (n = 16), and vestibular vertigo (eg, unilateral vestibular paresis, Meniere's disease) (n = 16) to test the hypothesis that a set of distinct symptoms can characterize cervical vertigo. Responses between the three diagnostic groups were compared to identify questions which differentiated patients based on their symptoms.

Results: Eight questions were successful in differentiating vestibular vertigo from migraine and cervical vertigo. Symptoms endorsed by subjects with cervical vertigo overlapped substantially with subjects with well-established vestibular disturbances as well as symptoms of subjects with migraine. Twenty-seven percent of cervical vertigo subjects reported having true vertigo, 50% having headache, and 94% having neck pain.

Conclusion: Lacking knowledge of neck disturbance, the symptoms we elicited in our questionnaire suggest that cervical vertigo subjects may resemble migraine subjects who also have evidence of neck injury. Whether or not subjects with "cervical vertigo" also overlap with other diagnoses defined by a combination of symptoms and exclusion of objective findings such as chronic subjective dizziness and other variants of psychogenic dizziness remain to be established.

Level of Evidence: IV.

HEADACHE and MIGRAINE (Continued)

The influence of rapid eye movement sleep deprivation on nociceptive transmission and the duration of facial allodynia in rats: a behavioral and Fos immunohistochemical study.

Kim SH[1], Park JY[1], Shin HE[1], Lee SB[1], Ryu DW[1], Kim TW[2], Park JW[3].

J Headache Pain. **2019 Mar 1**;20(1):21. doi: 10.1186/s10194-019-0977-0. PMID: 30823867.

BACKGROUND: Disrupted sleep is associated with a reciprocal influence on headaches and is one of the contributing factors in the process of chronicity. The goal of the present study was to investigate the influence of sleep on headaches using animal rapid eye movement (REM) sleep deprivation and supradural capsaicin infusion models.

METHOD: Sprague-Dawley rats underwent REM sleep deprivation (REMSD) for 96 h. The sensory threshold to mechanical stimuli, assessed by the von Frey monofilament test, was measured during the REMSD period. Additionally, the Fos protein expression level was measured in the trigeminocervical complex, periaqueductal gray, and hypothalamus. Following supradural infusion of capsaicin, we evaluated the duration of facial allodynia for 28 days after REMSD.

RESULTS: After REMSD, the sensory threshold to mechanical stimuli was significantly decreased ($p < 0.01$) and Fos-positivity in the posterior ($p = 0.010$) and dorsomedial hypothalamus ($p = 0.024$), ventrolateral periaqueductal gray ($p = 0.016$), and superficial layer of the trigeminocervical complex ($p = 0.019$) were significantly increased. The duration of facial allodynia induced by supradural capsaicin infusion was significantly longer in the REM sleep deprivation and capsaicin infusion group (Day 10 PSD vs. Day 25 PSD).

CONCLUSION: The present study demonstrates that REM sleep deprivation increased nociceptive transmission from trigeminal nerve endings. Furthermore, it suggests that sleep deprivation may contribute to the chronicity of facial allodynia.

Non-invasive neuromodulation for migraine and cluster headache: a systematic review of clinical trials.

Reuter U[1], McClure C[2], Liebler E[3], Pozo-Rosich P[4,5].

J Neurol Neurosurg Psychiatry. **2019 Mar 1**. pii: jnnp-2018-320113. doi: 10.1136/jnnp-2018-320113. PMID: 30824632. [Epub ahead of print]

Non-invasive neuromodulation therapies for migraine and cluster headache are a practical and safe alternative to pharmacologics. Comparisons of these therapies are difficult because of the heterogeneity in study designs. In this systematic review of clinical trials, the scientific rigour and clinical relevance of the available data were assessed to inform clinical decisions about non-invasive neuromodulation. PubMed, Cochrane Library and ClinicalTrials.gov databases and the WHO's International Clinical Trials Registry Platform were searched for relevant clinical studies of non-invasive neuromodulation devices for migraine and cluster headache (1 January 1990 to 31 January 2018), and 71 were identified. This analysis compared study designs using recommendations of the International Headache Society for pharmacological clinical trials, the only available guidelines for migraine and cluster headache. Non-invasive vagus nerve stimulation (nVNS), single-transcranial magnetic stimulation and external trigeminal nerve stimulation (all with regulatory clearance) were well studied compared with the other devices, for which studies frequently lacked proper blinding, sham controls and sufficient population sizes. nVNS studies demonstrated the most consistent adherence to available guidelines. Studies of all neuromodulation devices should strive to achieve the same high level of scientific rigour to allow for proper comparison across devices. Device-specific guidelines for migraine and cluster headache will be soon available, but adherence to current guidelines for pharmacological trials will remain a key consideration for investigators and clinicians.

HEADACHE and MIGRAINE (Continued)

Erenumab: A First-in-Class Monoclonal Antibody for Migraine Prevention.

Garland SG[1], Smith SM[2], Gums JG[2].

Ann Pharmacother. **2019 Feb 27**:1060028019835166. doi: 10.1177/1060028019835166. PMID: 30813769. [Epub ahead of print]

OBJECTIVE: To review the pharmacology, efficacy, and safety of the calcitonin gene-related peptide (CGRP) inhibitor erenumab for migraine preventive therapy.

DATA SOURCES: A MEDLINE/PubMed search (January 2000 to January 2019) was conducted using the keywords erenumab-aooe, erenumab, migraine, migraine prophylaxis, migraine prevention, and chronic migraine. Additional articles were identified by hand from references.

STUDY SELECTION AND DATA EXTRACTION: We included English-language articles (excluding poster presentations) evaluating erenumab pharmacology, efficacy, or safety in humans for migraine prevention.

DATA SYNTHESIS: Erenumab is a CGRP inhibitor that inhibits vasodilation in response to acute migraines, which decreases pain perception during the migraine. Erenumab efficacy and safety has only been compared with placebo, but its reduction in monthly migraine days (MMDs) and medication response (≥50% reduction in MMDs) are comparable to current recommended off-label therapies for migraine prevention in short-term treatment studies. Additionally, erenumab is associated with low adverse event burden with no difference found compared with placebo per published clinical trials. Relevance to Patient Care and Clinical Practice: Erenumab is the first medication approved in the United States for the prevention of migraines in adults. No head-to-head data are available, but existing data suggest that erenumab is at least as effective as current off-label products and with reduced adverse effects.

CONCLUSION: Erenumab is an effective once-monthly injectable agent for migraine prevention in patients with chronic or episodic migraine. It is also effective for patients who have previously failed migraine preventive therapy. Erenumab has a favorable adverse effect profile, which may improve patient adherence.

Chinese herbal medicine for headache: A systematic review and meta-analysis of high-quality randomized controlled trials.

Shi YH[1], Wang Y[1], Fu H[1], Xu Z[1], Zeng H[2], Zheng GQ[3].

Phytomedicine. **2018 Dec 31**;57:315-330. doi: 10.1016/j.phymed.2018.12.039. PMID: 30807986. [Epub ahead of print]

BACKGROUND: Chinese herbal medicines (CHMs) are widely used to relieve headache in Asia. However, it is uncertain whether there is robust evidence on the effects of CHMs for headache.

PURPOSE: To assess the effectiveness and safety of CHMs for headache using systematic review of high-quality randomized controlled trials (RCTs).

METHODS: Electronic search was conducted on six databases from inception to January 2018. We included the RCTs that met the requirement of at least 4 out of the 7 domains according to the Cochrane risk of bias tool.

RESULTS: Thirty RCTs with 3447 subjects were ultimately included for analysis and all trials were conducted in Asia. Meta-analysis showed that CHMs monotherapy were superior to placebo in reducing headache frequency [SMD -0.48 (95% CI -0.76, -0.20); $p < 0.01$], headache days [SMD -0.29 (95% CI -0.45, -0.13); $p < 0.01$], headache duration[SMD -0.58 (95% CI -0.81, -0.36); $p < 0.01$], headache intensity [SMD -0.42 (95% CI -0.62, -0.23); $p < 0.01$] and analgesic consumption [SMD -0.36 (95% CI -0.52, -0.21); $p < 0.01$] and improving clinical efficacy rate ($p < 0.01$). Similarly, CHMs monotherapy were superior to western conventional medicines (WCMs) in headache frequency [SMD -0.57 (95% CI -0.84, -0.29); $p < 0.01$], headache days ($p < 0.01$), analgesic consumption [SMD -1.63 (95% CI -1.98, -1.28); $p < 0.01$], headache intensity [SMD -0.81 (95% CI -1.06, -0.57); $p < 0.01$], and clinical efficacy rate [RR 1.24 (95% CI 1.18, 1.31); $p < 0.01$], except reducing headache duration ($p > 0.05$). CHMs adjunct therapy can improve clinical efficacy rate compared with WCMs alone [RR 1.15 (95% CI 1.09, 1.22); $p < 0.01$]. Meanwhile, CHMs had fewer adverse events than that of controls.

CONCLUSION: The findings supported, at least to an extent, the use of CHM for headache patients; however, we should treat the results cautiously because the clinical heterogeneity.

CHRONIC PAIN

Predictors of chronic pain intensity, spread, and sensitivity in the general population: A two-year follow-up study from the SWEPAIN cohort.

Larsson B[1], Dragioti E, Grimby-Ekman A, Gerdle B, Björk J.

J Rehabil Med. **2019 Feb 28**. doi: 10.2340/16501977-2519. PMID: 30815707. [Epub ahead of print]

OBJECTIVE: To determine whether the intensity, spread and sensitivity of chronic pain can be predicted using demographic features, socioeconomic conditions and comorbidities.

DESIGN: A longitudinal study design was employed. Data was collected at baseline and at 2-year follow-up.

SETTING: General population in south-eastern Sweden.

SUBJECTS: A representative stratified random sample of 34,000 individuals, between 18 and 85 years of age, selected from a sampling frame of 404,661 individuals based on the Swedish Total Population Register.

METHODS: Eligible individuals were sent postal surveys in 2013 and 2015. The 2 surveys included the same questions about basic demographic data, comorbidities, and chronic pain intensity, spread and sensitivity.

RESULTS: Several socio-demographic features and comorbidities at baseline were significant predictors of characteristics of pain (intensity, spread and sensitivity) at the 2-year follow-up. When characteristics of pain at baseline were included in the regression analyses they were relatively strong significant predictors of characteristics of pain after 2 years. After this adjustment there were fewer socio-demogra-phic and comorbidity predictors; the effect estimates for those significant predictors had decreased.

CONCLUSION: Clinical assessment should focus on several characteristics of pain and include a broad medical screening to capture the overall burden of pain in adults from a longitudinal perspective.

Health-Related Quality of Life among Chronic Opioid Users, Nonchronic Opioid Users, and Nonopioid Users with Chronic Noncancer Pain.

Hayes CJ[1,2], Li X[3], Li C[1], Shah A[1] , Kathe N[1], Bhandari NR[1], Payakachat N[1].

Health Serv Res. **2018 Oct**;53(5):3329-3349. doi: 10.1111/1475-6773.12836. PMCID: PMC6153159. PMID: 29479700. Epub 2018 Feb 25.

OBJECTIVE: Evaluate the association between opioid therapy and health-related quality of life (HRQoL) in participants with chronic, noncancer pain (CNCP).

DATA SOURCES:

Medical Expenditure Panel Survey Longitudinal, Medical Conditions, and Prescription Files.

STUDY DESIGN: Using a retrospective cohort study design, the Mental Health Component (MCS12) and Physical Health Component (PCS12) scores of the Short Form-12 Version 2 were assessed to measure mental and physical HRQoL.

DATA COLLECTION: Chronic, noncancer pain participants were classified as chronic, nonchronic, and nonopioid users. One-to-one propensity score matching was employed to match chronic opioid users to nonchronic opioid users plus nonchronic opioid users and chronic opioid users to nonopioid users.

PRINCIPAL FINDINGS: A total of 5,876 participants were identified. After matching, PCS12 was not significantly different between nonchronic versus nonopioid users (LSM Diff = -0.98, 95% CI: -2.07, 0.10), chronic versus nonopioid users (LSM Diff = -2.24, 95% CI: -4.58, 0.10), or chronic versus nonchronic opioid users (LSM Diff = -2.23, 95% CI: -4.53, 0.05). Similarly, MCS12 was not significantly different between nonchronic versus nonopioid users (LSM Diff = 0.76, 95% CI: -0.46, 1.98), chronic versus nonopioid users (LSM Diff = 1.08, 95% CI: -1.26, 3.42), or chronic versus nonchronic opioid users (LSM Diff = -0.57, 95% CI: -2.90, 1.77).

CONCLUSIONS: Clinicians should evaluate opioid use in participants with CNCP as opioid use is not correlated with better HRQoL.

CHRONIC PAIN (Continued)

Analysis of Anxiety, Depression and Aggression in Patients Attending Pain Clinics.

Kosson D[1], Malec-Milewska M[2], Gałązkowski R[3], Rzońca P[4].

Int J Environ Res Public Health. **2018 Dec 18**;15(12). pii: E2898. doi: 10.3390/ijerph15122898. PMID: 30567323.

The aim of the study was to measure the frequency of such emotional disturbances as anxiety, depression and aggression among patients treated in a pain clinic, as well as assess the factors contributing to such disorders. Research was conducted from January 2014 to April 2018 and involved patients treated in two pain clinics in the city of Warsaw, Poland. The study used the Hospital Anxiety and Depression Scale-Modified Version (HADS-M) and the Numerical Rating Scale (NSR). 1025 patients were recruited. The main reasons for their attending the pain clinic were osteoarticular pain (43.61%) and neuropathic pain (41.56%). Emotional disturbances in the form of anxiety were diagnosed in 32.39% of all the patients, depression in 17.85%, and aggression in 46.15%. The factors determining the level of anxiety in the study group were: sex, age, pain intensity and the lack of pharmacological treatment. Depression was determined by sex, pain intensity and the time of treatment in the clinic, while aggression by age and pain intensity.

Conditioned Pain Modulation in Sexual Assault Survivors.

Hellman N[1], Sturycz CA[1], Lannon EW[1], Kuhn BL[1], Güereca YM[1], Toledo TA[1], Payne MF[1], Huber FA[1], Demuth M[1], Palit S[1], Shadlow JO[1], Rhudy JL[2].

J Pain. **2019 Feb 27**. pii: S1526-5900(18)30673-4. doi: 10.1016/j.jpain.2019.02.012. PMID: 30825639. [Epub ahead of print]

Sexual assault (SA) is associated with increased risk for chronic pain, but the mechanisms for this relationship are poorly understood. To explore whether disrupted descending inhibition is involved, this study used a conditioned pain modulation (CPM) task to study inhibition of pain and the nociceptive flexion reflex (NFR; a correlate of spinal nociception) in 32 pain-free SA survivors. This group was compared to 32 pain-free, trauma-exposed persons without SA (no-SA group) and a group of 40 pain-free persons who reported no trauma exposure (no-TE). CPM was assessed from painful electric stimulations (test stimulus) delivered to the ankle before, during, and after participants submerged their hand in painful 10°C water (conditioning stimulus). Pain ratings and NFR were assessed in response to test stimuli. All groups demonstrated significant inhibition of pain during CPM. However, only the no-TE group demonstrated significant inhibition of NFR. The no-SA group showed no inhibition of NFR, whereas the SA group showed significant facilitation of NFR. These findings suggest that trauma exposure may impair inhibitory cerebrospinal circuits, but that SA may specifically promote facilitation of spinal nociception. Perspective: This study suggests trauma exposure disrupts cerebrospinal inhibition of spinal nociception but that exposure to sexual assault further promotes chronic pain risk by facilitating spinal nociception. This help may help elucidate the pain risk mechanisms in trauma survivors.

Systematic review of pharmacological therapies for the management of ischaemic pain in patients with non-reconstructable critical limb ischaemia.

Laoire ÁN[1], Murtagh FEM[2].

BMJ Support Palliat Care. **2018 Dec**;8(4):400-410. doi: 10.1136/bmjspcare-2017-001359. PMCID: PMC6287571. PMID: 28835456. Epub 2017 Aug 23.

BACKGROUND: Critical limb ischaemia (CLI) is a severe manifestation of peripheral arterial disease, characterised by chronic ischaemic rest pain, ulcers or gangrene. Management of ischaemic pain is challenging in patients with no options for revascularisation and optimal pharmacological therapies have not been established.

OBJECTIVES: To identify and evaluate the effectiveness of pharmacological therapies to treat ischaemic pain secondary to non-reconstructable CLI.

METHODS: This systematic review was reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. Comprehensive searches of three electronic databases, a PubMed-related articles link search, grey literature search and hand-searches of the bibliographies of relevant papers and textbooks were performed. Studies recruiting adult patients with CLI of any aetiology were eligible for inclusion. Surgical and revascularisation procedures, and all invasive interventions were excluded.

RESULTS: Of 792 studies, six met full inclusion criteria. These studies researched the use of intravenous lidocaine, intravenous ketamine, oral gabapentin and the combination of transdermal buprenorphine and epidural morphine/ropivacaine infusion. All studies showed an improvement in severity of ischaemic pain in CLI but with varying side effect profiles and quality. The extracted studies showed substantial heterogeneity and therefore a meta-analysis was not performed.

CONCLUSION: The pharmacological management of pain secondary to non-reconstructable CLI is a challenging review topic. No recommendations of pharmacological agents can be made following this review but a number of novel approaches to manage pain in this cohort have shown positive results and require further investigation.

CHRONIC PAIN (Continued)

Effects of yoga on patients with chronic nonspecific neck pain: A PRISMA systematic review and meta-analysis.

Li Y[1,2], Li S[3], Jiang J[4], Yuan S[1,2].

Medicine (Baltimore). **2019 Feb**;98(8):e14649. doi: 10.1097/MD.0000000000014649. PMID: 30813206

BACKGROUND: Chronic nonspecific neck pain (CNNP) has a high prevalence and is more common among younger people. Clinical practice suggests that yoga is effective in relieving chronic pain.

OBJECTIVES: This meta-analysis aimed to quantitatively summarize the efficacy of yoga for treating CNNP.

DATA SOURCES: We searched for trials in the electronic databases from their inception to January 2019. English databases including PubMed, MEDLINE, Cochrane Library, Embase, Scopus, the Cochrane Central Register of Controlled Trials, and Ind Med; Chinese databases including China National Knowledge Infrastructure (CNKI), WanFang Database, and VIP Information. We also conducted a manual search of key journals and the reference lists of eligible papers to identify any potentially relevant studies we may have missed. We placed no limitations on language or date of publication.

STUDY ELIGIBILITY CRITERIA: We included only randomized controlled trials (RCTs) and q-RCTs evaluating the effects of yoga on patients with CNNP. The primary outcomes for this review were pain and disability, and the secondary outcomes were cervical range of motion (CROM), quality of life (QoL), and mood.

PARTICIPANTS AND INTERVENTIONS: Trails that examined the clinical outcomes of yoga intervention in adults with CNNP compared with those of other therapies except yoga (e.g., exercise, pilates, usual care, et al) were included.

STUDY APPRAISAL AND SYNTHESIS METHODS: Cochrane risk-of-bias criteria were used to assess the methodological quality, and RevMan 5.3 software was used to conduct the meta-analysis.

RESULTS: A total of 10 trials (n=686) comparing yoga and interventions other than yoga were included in the meta-analysis. The results show that yoga had a positive effects on neck pain intensity (total effect: SMD=-1.13, 95% CI [-1.60, -0.66], Z=4.75, P<.00001), neck pain-related functional disability (total effect: SMD=-0.92, 95% CI [-1.38, -0.47], Z=3.95, P<.0001), CROM (total effect: SMD=1.22, 95% CI [0.87, 1.57], Z=6.83, P<.00001), QoL (total effect: MD=3.46, 95% CI [0.75, 6.16], Z=2.51, P=.01), and mood (total effect: SMD=-0.61, 95% CI [-0.95, -0.27], Z=3.53, P=.0004).

CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: It was difficult to make a comprehensive summary of all the evidence due to the different session and duration of the yoga interventions, and the different outcome measurement tools in the study, we draw a very cautious conclusion that yoga can relieve neck pain intensity, improve pain-related function disability, increase CROM, improve QoL, and boost mood. This suggests that yoga might be an important alternative in the treatment of CNNP.

SYSTEMATIC REVIEW REGISTRATION NUMBER: Details of the protocol for this systematic review and meta-analysis were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42018108992.

Ultramicronized Palmitoylethanolamide (um-PEA) as add-on Treatment in Fibromyalgia Syndrome (FMS): Retrospective Observational Study on 407 Patients.

Schweiger V[1], Martini A[1], Bellamoli P[1], Donadello K[1], Schievano C[2], Balzo GD[3], Sarzi-Puttini P[4], Parolini M[1], Polati E[1].

CNS Neurol Disord Drug Targets. **2019 Feb 27**. doi: 10.2174/1871527318666190227205359. PMID: 30827269. [Epub ahead of print]

BACKGROUND: fibromyalgia syndrome is a chronic multifaceted disease characterized by widespread pain, muscle stiffness, fatigue, unrefreshing sleep and cognitive disorders. To date, no medication has been shown to significantly improve pain, associated symptoms and Quality of Life in fibromyalgic patients.

METHODS: In this retrospective observational study, we analyzed data regarding 407 patients with diagnosis of fibromyalgia syndrome who between 2013 and 2016 have been prescribed orally ultramicronized palmitoylethanolamide tablets (Normast® Epitech Group SpA, Saccolongo, Italy) regardless of the concomitant pharmacological therapy (add-on treatment).

RESULTS: Regarding efficacy, in the whole eligible population in the 359 analyzed patients, the change over time in Visual Analogue Scale pain score was statistically significant, ranging from 75.84 (±15.15) to 52.49 (±16.73) (p<0.001). Regarding quality of life, the change from baseline to the end of observation over time in Fibromyalgia Impact Questionnaire score was statistically significant, ranging from 68.4 (±14.1) to 49.1 (±19.6) (p<0.001). In the whole treated population, only 36 patients (13,7%) reported Adverse Events predominantly of gastrointestinal type (diarrhea, dyspepsia, bloating, constipation, vomiting). Globally, 151 patients (57,63%) leave the treatment for lack of efficacy.

CONCLUSION: The results of ultramicronized palmitoylethanolamide treatment in this retrospective analysis may seem irrelevant but in represent an important step for the development of a new and well tolerated therapy for fibromyalgia syndrome, mostly suitable for these patients who need long-term treatments even a modest effect, especially if not conditioned by relevant side effects, can be significant for patients. Further methodologically stronger studies will be necessary to validate our observation.

OTHER RESEARCH OF INTEREST

Daily life physical activity in patients with chronic stage IV sarcoidosis: A multicenter cohort study.

Froidure S[1], Kyheng M[2], Grosbois JM[3], Lhuissier F[4,5] , Stelianides S[6], Wemeau L[1], Wallaert B[1].

Health Sci Rep. **2019 Jan 15**;2(2):e109. doi: 10.1002/hsr2.109. PMCID: PMC6375542. PMID: 30809595. eCollection 2019 Feb.

Background and Objectives: Little is known about the consequences of chronic sarcoidosis on daily life physical activity (DL_{PA}). The aim of this prospective study was to measure DL_{PA} in patients with chronic sarcoidosis and to determine its relationship to clinical and functional parameters.

Methods: Fifty-three patients with chronic sarcoidosis and 28 healthy control subjects were enrolled in this multicenter prospective study. Two markers of DL_{PA} (number of steps walked per day [SPD]) and total daily energy expenditure (TEE) were assessed for five consecutive days with a physical activity monitor. Pulmonary function, aerobic capacity (maximal oxygen uptake [VO_2max]), exercise capacity (6-min walk test [6MWT]), and quality of life (self-reported questionnaires) were also evaluated. Comparisons of DL_{PA} parameters between the two groups were performed using an analysis of covariance adjusted for age, sex, and body mass index (BMI). Relationships between DL_{PA} parameters and patient characteristics were assessed in multivariable linear regression models.

Results: Patients with sarcoidosis walked significantly fewer SPD than did the control subjects (6395 ± 4119 and 11 817 ± 3600, respectively; $P < 0.001$ after adjustment for age, BMI, and sex). TEE was not significantly different between patients with sarcoidosis and healthy controls (median [interquartile range]: 2369 [2004-2827] and 2387 [2319-2876] kcal/day, respectively, $P = 0.054$ adjusted for age, BMI, and sex). SPD showed significant positive correlations with 6MWT distance (Pearson's correlation, $r = 0.32$, 95% confidence intervals [95%CI] = 0.06, 0.55; $P = 0.019$), VO_2max ($r = 0.44$, 95%CI = 0.17, 0.65; $P = 0.002$), and Visual Simplified Respiratory Questionnaire score ($r = 0.44$, 95%CI = 0.19, 0.64; $P = 0.001$), and a significant negative correlation with modified Medical Research Council questionnaire score ($r = -0.38$, 95%CI = -0.60, -0.10; $P = 0.009$). TEE was significantly correlated with BMI ($r = 0.38$, 95%CI = 0.13, 0.59; $P = 0.004$), forced expiratory volume in 1 second ($r = 0.55$, 95%CI = 0.33, 0.71; $P < 0.001$), total lung capacity ($r = 0.44$, 95%CI = 0.18, 0.64; $P = 0.001$), and forced vital capacity ($r = 0.56$, 95%CI = 0.34, 0.72; $P < 0.001$). In multivariable analysis, SPD remained associated only with VO_2max.

Conclusion: Patients with chronic sarcoidosis appear to have reduced DL_{PA} mainly because of compromised VO_2max.

Structural and cognitive correlates of fatigue in progressive multiple sclerosis.

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Neurol Res. **2019 Feb**;41(2):168-176. doi: 10.1080/01616412.2018.1547813. PMID: 30513278. Epub 2018 Dec 4.

BACKGROUND: Fatigue in multiple sclerosis (MS) is a debilitating symptom and experienced by most patients. In recent studies investigating this phenomenon, the majority of patients had a relapsing-remitting disease course.

METHODS: Patients with progressive MS participating in one of three treatment trials during a period from 2010 to 2014 were included. Fatigue was assessed with the Fatigue Scale for Motor and Cognitive Functions (FSMC) and patients were further examined with a cognitive test battery, including Symbol Digit Modalities Test (SDMT), and 3 T MRI with subsequent quantitative analyses of 13 cortical regions of interest, deep grey matter and lesion volume.

RESULTS: Twenty-two patients were enrolled. The thickness of the pre-central gyrus correlated significantly with motor fatigue. We found only a non-significant trend towards a correlation between cognitive fatigue and the thickness of the pre-central gyrus, the parietal inferior supra-marginal gyrus and the opercular part of the inferior frontal gyrus. 36% of participants had impaired processing speed and 9% had normal function on all tests. The scores on the FSMC-cognitive scale were related to performance on SDMT.

CONCLUSION: In this exploratory study of patients with progressive MS, fatigue was related to processing speed. Motor fatigue was also related to the cortical thickness of the primary motor cortex and there was a trend towards a relationship between cognitive fatigue and the thickness of cortical areas involved in attentional processes. Additional studies are needed to further elucidate the relationship between regional cortical atrophy, cognitive functioning and the perception of fatigue.

OTHER RESEARCH OF INTEREST (Continued)

Neuropsychiatric Outcomes in UK Military Veterans With Mild Traumatic Brain Injury and Vestibular Dysfunction.

Denby E[1], Murphy D, Busuttil W, Sakel M, Wilkinson D.

J Head Trauma Rehabil. **2019 Feb 27**. doi: 10.1097/HTR.0000000000000468. PMID: 30829817. [Epub ahead of print]

OBJECTIVE: To estimate the frequency of vestibular dysfunction following blunt, blast, and combined blunt and blast mild traumatic brain injury (mTBI) and thereon assess the long-term impact of vestibular dysfunction on neurobehavioral function and disability independently of comorbid psychiatric symptoms.

SETTING: Combat Stress residential and Veterans' Outreach drop-in centers for psychological support.

PARTICIPANTS: One hundred sixty-two help-seeking UK military veterans.

MAIN MEASURES: Self-reported frequency and severity of mTBI (using the Ohio State TBI Identification Method), Vertigo Symptom Scale, PTSD Checklist for DSM-5, Kessler Psychological Distress Scale (K10), Neurobehavioral Symptom Inventory, Headache Impact Test (HIT6), Memory Complaints Inventory, World Health Organization Disability Assessment Schedule II short version (WHODAS 2.0).

RESULTS: Seventy-two percent of the sample reported 1 or more mTBIs over their lifetime. Chi-square analyses indicated that vestibular disturbance, which affected 69% of participants, was equally prevalent following blunt (59%) or blast (47%) injury and most prevalent following blunt and blast combined (83%). Mediation analysis indicated that when posttraumatic stress disorder, depression, and anxiety were taken into account, vestibular dysfunction in participants with mTBI was directly and independently associated with increased postconcussive symptoms and functional disability.

CONCLUSION: Vestibular dysfunction is common after combined blunt and blast mTBI and singularly predictive of poor long-term mental health. From a treatment perspective, vestibular rehabilitation may provide relief from postconcussive symptoms other than dizziness and imbalance.

Teleneurology service provided via tablet technology: 3-year outcomes and physician satisfaction.

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Rural Remote Health. **2019 Mar**;19(1):4743. doi: 10.22605/RRH4743. PMID: 30825873. Epub 2019 Mar 4.

INTRODUCTION: This study aimed to demonstrate that teleneurology consultations conducted via tablet technology are an efficient and cost-effective means of managing acute neurologic emergencies at community-based hospitals and that utilizing such technology yields high community physician satisfaction.

METHOD: During a 39-month period, Vanderbilt University Medical Center in Tennessee USA, provided teleneurology services to 10 community-based hospitals that lacked adequate neurology coverage. Hospitalists at one community-based hospital were not comfortable treating any patient with a neurologic symptom, resulting in 100% of those patients being transferred. This facility now retains more than 60% of neurology patients. For less than US$1200, these hospitals were able to meet the only capital expenditure required to launch this service: the purchase of handheld tablet computers. Real-time teleneurology consultations were conducted via tablet using two-way video conferencing, radiologic image sharing, and medical record documentation. Community physicians were regularly surveyed to assess satisfaction.

RESULTS: From February 2014 to May 2017, 3626 teleneurology consultations were conducted. Community physicians, in partnership with neurologists, successfully managed 87% of patients at the community-based hospital. Only 13% of patients required transfer to another facility for a higher level of care. The most common diagnoses included stroke (34%), seizure (11%), and headache/migraine (6%). The average time for the neurologist to answer a request for consultation page and connect with the community physician was 10.6 minutes. Ninety-one percent of community physicians were satisfied or somewhat satisfied with the overall service.

CONCLUSION: In the assessment of neurology patients, tablets are a more cost-effective alternative to traditional telehealth technologies. The devices promote efficiency in consultations through ease of use and low transfer rates, and survey results indicate community physician satisfaction.

OTHER RESEARCH OF INTEREST (Continued)

Towards integrated medical and mental healthcare in the inpatient setting: what is the role of psychology?

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Int Rev Psychiatry. **2019 Mar 1**:1-14. doi: 10.1080/09540261.2018.1552125. PMID: 30821187. [Epub ahead of print]

Integrated medical and psychiatric hospital units hold great promise for improving the value and quality of care for patients with severe mental illness and concomitant acute medical needs. It is important to explore the utility of providing a range of multidisciplinary inpatient services to meet patients' complex needs. Within this context, services typically provided by psychologists have received little research attention. To address this gap in the literature, this study assessed inpatient clinicians' perceptions of the need for specific behavioural services on a medical psychiatric unit, exploring their overlap with established psychological services. Results indicate the potential utility of specific psychological services, including psychological assessments, direct psychosocial interventions, and psychoeducational training. While reimbursement and billing barriers still exist for psychologists to be routinely incorporated into hospital settings, the movement towards value-based care could provide the opportunity to think about the value added. Embedding evidence-based psychological services has the potential to promote high quality, well-rounded care that aligns with the established mission of multidisciplinary teamwork on integrated medical and psychiatric inpatient units.

Chronic pain, functional status, and life satisfaction are associated with patients living with HIV discussing advanced care planning with their family or friends.

Hansen ED[1], Mitchell MM[2], Cruz Oliver DM[3], Alghanim FA[4], Walter M[5], Case AA[5], Smith T[3], Knowlton AR[2].

J Pain Symptom Manage. **2019 Feb 25**. pii: S0885-3924(19)30096-X. doi: 10.1016/j.jpainsymman.2019.02.018. PMID: 30818027. [Epub ahead of print]

CONTEXT: In the era of effective antiretroviral therapy, persons living with HIV/AIDS (PLWHA) are living longer, transforming HIV into a serious chronic illness, warranting discussions between patients and their loved ones about advanced care planning (ACP). Evidence is needed on factors associated with patients' likelihood to discuss ACP with loved ones.

OBJECTIVES: To further characterize factors associated with successful ACP in PLWHA with their loved ones, we examined associations between patients having ACP discussions with the need for assistance with personal care, chronic pain, life satisfaction, prior family disagreements over healthcare decisions, sex, age, and interference in daily routines due to memory problems.

METHODS: Data were from the Affirm Care study (N=370), which examined social and environmental factors associated with health outcomes among PLWHA and their informal caregivers.

RESULTS: Slightly more than half of respondents discussed ACP with loved ones (57%). In adjusted analysis, higher levels of chronic pain (odds ratio (OR) =2.09, p=0.045), needing assistance with personal care (OR=1.63, p=0.023), greater life satisfaction (OR 1.02, p=0.002), prior family arguments over healthcare decisions (OR=2.80, p<0.001) and female sex (OR 2.22, p=0.001) were associated with higher odds of discussing ACP with loved ones, while age, drug use, education level, depression, and memory problems were non-significant.

CONCLUSION: These results suggest that interventions to increase ACP among PLWHA and their loved ones should target males. The findings also suggest PLWHA with chronic pain, the need for assistance with personal care, and those with a history of prior family arguments over healthcare decisions may be primed for ACP.

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