GULF WAR ILLNESS

Exercise - induced changes in cerebrospinal fluid miRNAs in Gulf War Illness, Chronic Fatigue Syndrome and sedentary control subjects.

Baraniuk JN[1], Shivapurkar N[2].

Sci Rep. **2017 Nov 10**;7(1):15338. doi: 10.1038/s41598-017-15383-9.

Gulf War Illness (GWI) and Chronic Fatigue Syndrome (CFS) have similar profiles of pain, fatigue, cognitive dysfunction and exertional exhaustion. Post-exertional malaise suggests exercise alters central nervous system functions. Lumbar punctures were performed in GWI, CFS and control subjects after (i) overnight rest (nonexercise) or (ii) submaximal bicycle exercise. Exercise induced postural tachycardia in one third of GWI subjects (Stress Test Activated Reversible Tachycardia, START). The remainder were Stress Test Originated Phantom Perception (STOPP) subjects. MicroRNAs (miRNA) in cerebrospinal fluid were amplified by quantitative PCR. Levels were equivalent between nonexercise GWI (n = 22), CFS (n = 43) and control (n = 22) groups. After exercise, START (n = 22) had significantly lower miR-22-3p than control (n = 15) and STOPP (n = 42), but higher miR-9-3p than STOPP. All post-exercise groups had significantly reduced miR-328 and miR-608 compared to nonexercise groups; these may be markers of exercise effects on the brain. Six miRNAs were significantly elevated and 12 diminished in post-exercise START, STOPP and control compared to nonexercise groups. CFS had 12 diminished miRNAs after exercise. Despite symptom overlap of CFS, GWI and other illnesses in their differential diagnosis, exercise-induced miRNA patterns in cerebrospinal fluid indicated distinct mechanisms for post-exertional malaise in CFS and START and STOPP phenotypes of GWI.

CHRONIC FATIGUE SYNDROME

Vitamin D status in chronic fatigue syndrome/myalgic encephalomyelitis: a cohort study from the North-West of England.

Earl KE[1], Sakellariou GK[1,2], Sinclair M[1], Fenech M[1, 3], Croden F[4], Owens DJ[5], Tang J[6], Miller A[3], Lawton C[4], Dye L[4], Close GL[5], Fraser WD[6], McArdle A[1], Beadsworth MBJ[1,3].

BMJ Open. **2017 Nov 8**;7(11):e015296. doi: 10.1136/bmjopen-2016-015296.

OBJECTIVE: Severe vitamin D deficiency is a recognised cause of skeletal muscle fatigue and myopathy. The aim of this study was to examine whether chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with altered circulating vitamin D metabolites.

DESIGN: Cohort study.

SETTING: UK university hospital, recruiting from April 2014 to April 2015.

PARTICIPANTS: Ninety-two patients with CFS/ME and 94 age-matched healthy controls (HCs).

MAIN OUTCOME MEASURES: The presence of a significant association between CFS/ME, fatigue and vitamin D measures.

RESULTS: No evidence of a deficiency in serum total 25(OH) vitamin D (25(OH)D_2 and 25(OH)D_3 metabolites) was evident in individuals with CFS/ME. Liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis revealed that total 25(OH)D was significantly higher (p=0.001) in serum of patients with CFS/ME compared with HCs (60.2 and 47.3 nmol/L, respectively). Analysis of food/supplement diaries with WinDiets revealed that the higher total 25(OH) vitamin D concentrations observed in the CFS/ME group were associated with increased vitamin D intake through use of supplements compared with the control group. Analysis of Chalder Fatigue Questionnaire data revealed no association between perceived fatigue and vitamin D levels.

CONCLUSIONS: Low serum concentrations of total 25(OH)D do not appear to be a contributing factor to the level of fatigue of CFS/ME.

HEADACHE and MIGRAINE

CGRP and PTX3 as Predictors of Efficacy of Onabotulinumtoxin Type A in Chronic Migraine: An Observational Study.

Domínguez C[1], Vieites-Prado A[2], Pérez-Mato M[2], Sobrino T [2], Rodríguez-Osorio X[1], López A[1], Campos F[2], Martínez F[1], Castillo J[2], Leira R [1].

Headache. **2017 Nov 13**. doi: 10.1111/head.13211. [Epub ahead of print]

OBJECTIVE: The aim of this study is to find a relation between several biomarkers in peripheral blood and outcome after treatment with onabotulinumtoxin A (OnabotA).

BACKGROUND: OnabotA is an effective treatment in chronic migraine (CM). Different studies have tried to find predictors of response to treatment, either with clinical characteristics, neuroimaging features, or molecular biomarkers; however, it is still not possible to predict the individual outcome.

METHODS: We measured serum levels of biomarkers of inflammation (IL-6, IL-10, TNF-α, and hs-CRP), endothelial dysfunction (PTX3 and sTWEAK), blood-brain barrier disruption (cFN), brain damage (S100b, NSE), and trigemino-vascular activation (CGRP) by ELISA in a group of CM patients treated with OnabotA and healthy controls. After 24 weeks, patients were classified in two groups according to their outcome considering variations in headache frequency: nonresponders (nonimprovement or improvement <50%) and responders (improvement >50%). We compared baseline levels of biomarkers between these groups.

RESULTS: Sixty-two patients diagnosed with CM (IHS 2013 criteria) who fulfilled criteria for treatment with OnabotA and 24 healthy controls were included. Fifteen patients did not respond to treatment (24.2%) and 47 were responders (75.8%). Pentraxin 3 (PTX3) serum levels (1455.4 ± 487.5 pg/mL versus 720.3 ± 334.1 pg/mL, $P < .0001$) and calcitonin gene-related peptide (CGRP) serum levels (133.1 ± 86.6 ng/mL versus 58.2 ± 91.7 ng/mL, $P = .004$) were significantly higher in responders than nonresponders. Serum basal levels of PTX3 >1000 pg/mL (AUC 0.908; 95% CI: 0.827-0.990) and CGRP >50 ng/mL (AUC 0.800; 95% CI: 0.652-0.947) were associated with good response to OnabotA treatment.

CONCLUSIONS: These results show that molecular markers of trigeminovascular activation (CGRP) and endothelial dysfunction (PTX3) are associated with response to OnabotA and may act as new biomarkers for the selection of treatment in chronic migraineurs.

Heterogenous migraine aura symptoms correlate with visual cortex fMRI responses.

Arngrim N[1], Hougaard A[1], Ahmadi K[2], Vestergaard MB[3], Schytz HW[1], Amin FM[1], Larsson HBW[3], Olesen J[1], Hoffmann MB[2,4], Ashina M[1].

Ann Neurol. **2017 Nov 11**. doi: 10.1002/ana.25096. [Epub ahead of print]

OBJECTIVE: Migraine aura is sparsely studied due to the highly challenging task of capturing patients during aura. Cortical spreading depression (CSD) is likely the underlying phenomenon of aura. The possible correlation between the multifaceted phenomenology of aura symptoms and the effects of CSD on the brain has not been ascertained.

METHODS: Five migraine patients were studied during various forms of aura symptoms induced by hypoxia, sham or physical exercise and photostimulation. The blood oxygenation level-dependent (BOLD) functional MRI (fMRI) signal response to visual stimulation was measured in retinotopic mapping defined visual cortex area V1 - V4.

RESULTS: We found reduced BOLD response in patients reporting scotoma and increased response in patients who only experienced positive symptoms. Furthermore, patients with bilateral visual symptoms had corresponding bi-hemispherical changes in BOLD response.

INTERPRETATION: These findings suggest that different aura symptoms reflect different types of cerebral dysfunction, which correspond to specific changes in BOLD signal reactivity. Furthermore, we provide evidence of bilateral CSD recorded by fMRI during bilateral aura symptoms.

HEADACHE and MIGRAINE (Continued)

Decreased risk of dementia in migraine patients with traditional Chinese medicine use: a population-based cohort study.

Liu CT[1], Wu BY[1], Hung YC[1,2], Wang LY[3], Lee YY[3], Lin TK[4], Lin PY[5], Chen WF[6], Chiang JH[7,8], Hsu SF[9,10], Hu WL[1,11,12].

Oncotarget. **2017 Jul 8**;8(45):79680-79692. doi: 10.18632/oncotarget.19094. PMCID: PMC5668081. eCollection 2017 Oct 3.

Patients with migraine are reportedly at increased risk of developing dementia. We aimed to investigate the association between traditional Chinese medicine (TCM) use and dementia risk in migraine patients. This longitudinal cohort study used the Taiwanese National Health Insurance Research Database to identify 32,386 diagnosed migraine patients aged 20 years and above who received treatment from 1997 to 2010. To balance comparability between TCM users and non-TCM users, we randomly selected equal numbers from each group, and compared subgroups compiled based on combinations of age, sex, index year, and year of migraine diagnosis. All enrollees received follow-up until the end of 2013 to measure dementia incidence. We identified 1,402 TCM users and non-TCM users after frequency matching. A total of 134 subjects were newly diagnosed with dementia during the follow-up period. TCM users were significantly less likely to develop dementia than non-TCM users. The most frequently prescribed formulae and single Chinese herbal products were Jia-Wei-Xiao-Yao-San and Yan-Hu-Suo, respectively. This population-based study revealed a decreased dementia risk in migraine patients with TCM use. These findings may provide a reference for dementia prevention strategies, and help integrate TCM into clinical intervention programs that provide a favorable prognosis for migraine patients.

Salivary glutamate is elevated in individuals with chronic migraine.

Nam JH[1,2], Lee HS[1,3], Kim J[4], Kim J[5], Chu MK[6].

Cephalalgia. **2017 Jan 1**:333102417742366. doi: 10.1177/0333102417742366. [Epub ahead of print]

Background Glutamate has been implicated in migraine pathogenesis, and is elevated in the plasma, cerebrospinal fluid, and saliva in migraineurs. However, no comparison of glutamate levels among chronic migraine, episodic migraine and controls has been reported. The aim is to compare salivary glutamate levels of individuals with chronic migraine with those of individuals with episodic migraine and healthy controls. Methods We investigated salivary glutamate level of 46 women with chronic migraine, 50 women with episodic migraine, and 19 healthy controls via enzyme linked immunosorbent assay. Results The salivary glutamate level of the chronic migraine group (median and interquartile range, 20.47 [15.27-30.15] pmol/mg total protein) was significantly higher than those of the episodic migraine (16.17 [12.81-20.15] pmol/mg total protein, $p = 0.008$) and control (12.18 [9.40-16.24] pmol/mg total protein, $p = 0.001$) groups. The salivary glutamate level of the episodic migraine group was marginally elevated from that of the control group (post hoc $p = 0.016$). Thresholds of 16.58 and 17.94 pmol/mg total protein optimize the sensitivity and specificity to differentiate chronic migraine participants from healthy controls and episodic migraine participants, respectively. Conclusions Salivary glutamate level was elevated in chronic migraine participants. These data suggest that salivary glutamate level could be an indicator of CM.

Daily vision testing can expose the prodromal phase of migraine.

McKendrick AM[1], Chan YM[1], Vingrys AJ[1], Turpin A[2], Badcock DR[3].

Cephalalgia. **2017 Jan 1**:333102417741130. doi: 10.1177/0333102417741130. [Epub ahead of print]

Background Several visual tasks have been proposed as indirect assays of the balance between cortical inhibition and excitation in migraine. This study aimed to determine whether daily measurement of performance on such tasks can reveal perceptual changes in the build up to migraine events. Methods Visual performance was measured daily at home in 16 non-headache controls and 18 individuals with migraine using a testing protocol on a portable tablet device. Observers performed two tasks: luminance increment detection in spatial luminance noise and centre surround contrast suppression. Results Luminance thresholds were reduced in migraine compared to control groups ($p < 0.05$), but thresholds did not alter across the migraine cycle; while headache-free, centre-surround contrast suppression was stronger for the migraine group relative to controls ($p < 0.05$). Surround suppression weakened at around 48 hours prior to a migraine attack and strengthened to approach their headache-free levels by 24 hours post-migraine (main effect of timing, $p < 0.05$). Conclusions Daily portable testing of vision enabled insight into perceptual performance in the lead up to migraine events, a time point that is typically difficult to capture experimentally. Perceptual surround suppression of contrast fluctuates during the migraine cycle, supporting the utility of this measure as an indirect, non-invasive assay of the balance between cortical inhibition and excitation.

CHRONIC PAIN

The effect of pulsed electromagnetic frequency therapy on health-related quality of life in military service members with chronic low back pain.

Nayback-Beebe AM[1], Yoder LH[2], Goff BJ[3], Arzola S[4], Weidlich C[4].

Nurs Outlook. **2017 Sep - Oct**;65(5S):S26-S33. doi: 10.1016/j.outlook.2017.07.012. Epub 2017 Jul 20.

BACKGROUND: In the U.S. military, chronic low back pain is among the most frequent complaints for medical visits, lost work time, and attrition from active duty and the deployed setting by service members.

PURPOSE: The aim of this pilot study was to determine whether adjunctive treatment with pulsed electromagnetic frequency (PEMF) produced significant variability in chronic low back pain symptoms and secondary health-related quality of life, mental health and disability outcomes.

METHODS: Prospective, randomized pilot study with repeated measures at baseline, post-treatment, and 1 month follow-up for two groups: usual care (UC) vs. UC + PEMF.

FINDINGS: In a convenience sample of 75 service members, health-related quality of life mental and physical component scores were significant: $F(2, 104) = 4.20$, $p = .018$ ($\eta^2 = .075$) and $F(2, 104) = 4.75$, $p = .011$ ($\eta^2 = .084$), respectively; as was anxiety symptom severity: $F(2, 104) = 5.28$, $p = .007$ ($\eta^2 = .092$).

DISCUSSION AND RECOMMENDATIONS: Adjunctive treatment with PEMF demonstrated improvements in service members' overall physical health-related quality of life with expected, yet statistically nonsignificant improvements in reported pain and LBP-related disability. There were significant between group differences in anxiety symptom severity with higher symptoms reported by the UC + PEMF group, surprising findings that warrant further investigation.

Race and Ethnicity Do Not Clinically Associate with Quality of Life Among Patients with Chronic Severe Pain in a Federally Qualified Health Center.

Dhingra L[1,2], Schiller R[3,4], Teets R[3,4], Nosal S[3], Rodriguez S[1], Cruciani G[1], Barrett M[1], Ginzburg R[3,5], Ahmed E[1,5], Wasser T[6], Chen J[1], Shuman S[3], Crump C[3,4], Portenoy R[1,7].

Pain Med. **2017 May 10**. doi: 10.1093/pm/pnx040. [Epub ahead of print]

Objective: Previous research suggests that race/ethnicity predicts health-related quality of life (HRQL) in chronic pain populations but has not examined this in community settings. This study evaluated this association in 522 community-dwelling patients with chronic pain treated at a Federally Qualified Health Center (FQHC).

Design: Cross-sectional secondary analysis.

Setting: Six practice sites of an FQHC in New York.

Subjects: One hundred forty-two non-Hispanic blacks, 121 non-Hispanic whites, 219 Hispanics, and 40 classified as "other" with severe chronic pain.

Methods: Patients with chronic severe pain (three or more months with worst pain ≥ 4/10 or T-score > 60.5 on the Patient-Reported Outcomes Measurement Information System pain interference tool) were interviewed as part of a clinical trial. Race/ethnicity and other potential predictors of HRQL were assessed.

Results: Mean age was 53.0 years, and 70.1% were women; 62.8% earned less than $10,000 per year, and 22.8% were Spanish-speaking with low acculturation. Mean worst pain during the past week was 8.6/10, and 39.6% used opioids. In multivariate analyses, race/ethnicity was not significantly associated with mental HRQL. Hispanics had significantly lower physical HRQL than non-Hispanic whites or blacks, but this difference was not clinically meaningful (mean T-scores = 33.9 [Hispanics], 35.8 [non-Hispanic whites], and 35.6 [non-Hispanic blacks]). Mental HRQL was predicted by depression, anxiety, pain disability, income, and physical HRQL; physical HRQL was predicted by race/ethnicity, anxiety, pain disability, age, care satisfaction, and mental HRQL.

Conclusions: Race/ethnicity does not explain important variation in HRQL reported by diverse patients with chronic pain. Psychological distress, pain disability, age, and socioeconomic status predicted this health outcome. Future studies may clarify modifiers of these associations to guide treatment in FQHC populations.

CHRONIC PAIN (Continued)

Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial.

Deer TR[1], Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton AW, Burgher AH, Obray J, Scowcroft J, Golovac S, Kapural L, Paicius R, Kim C, Pope J, Yearwood T, Samuel S, McRoberts WP, Cassim H, Netherton M, Miller N, Schaufele M, Tavel E, Davis T, Davis K, Johnson L, Mekhail N.

Pain. **2017 Apr**;158(4):669-681. doi: 10.1097/j.pain.0000000000000814. PMCID: PMC5359787.

Animal and human studies indicate that electrical stimulation of dorsal root ganglion (DRG) neurons may modulate neuropathic pain signals. ACCURATE, a pivotal, prospective, multicenter, randomized comparative effectiveness trial, was conducted in 152 subjects diagnosed with complex regional pain syndrome or causalgia in the lower extremities. Subjects received neurostimulation of the DRG or dorsal column (spinal cord stimulation, SCS). The primary end point was a composite of safety and efficacy at 3 months, and subjects were assessed through 12 months for long-term outcomes and adverse events. The predefined primary composite end point of treatment success was met for subjects with a permanent implant who reported 50% or greater decrease in visual analog scale score from preimplant baseline and who did not report any stimulation-related neurological deficits. No subjects reported stimulation-related neurological deficits. The percentage of subjects receiving ≥50% pain relief and treatment success was greater in the DRG arm (81.2%) than in the SCS arm (55.7%, $P < 0.001$) at 3 months. Device-related and serious adverse events were not different between the 2 groups. Dorsal root ganglion stimulation also demonstrated greater improvements in quality of life and psychological disposition. Finally, subjects using DRG stimulation reported less postural variation in paresthesia ($P < 0.001$) and reduced extraneous stimulation in nonpainful areas ($P = 0.014$), indicating DRG stimulation provided more targeted therapy to painful parts of the lower extremities. As the largest prospective, randomized comparative effectiveness trial to date, the results show that DRG stimulation provided a higher rate of treatment success with less postural variation in paresthesia intensity compared to SCS.

Brain white matter changes associated with urological chronic pelvic pain syndrome: multisite neuroimaging from a MAPP case-control study.

Huang L[1], Kutch JJ, Ellingson BM, Martucci KT, Harris RE, Clauw DJ, Mackey S, Mayer EA, Schaeffer AJ, Apkarian AV, Farmer MA.

Pain. **2016 Dec**;157(12):2782-2791. PMCID: PMC5117992.

Clinical phenotyping of urological chronic pelvic pain syndromes (UCPPSs) in men and women have focused on end organ abnormalities to identify putative clinical subtypes. Initial evidence of abnormal brain function and structure in male pelvic pain has necessitated large-scale, multisite investigations into potential UCPPS brain biomarkers. We present the first evidence of regional white matter (axonal) abnormalities in men and women with UCPPS, compared with positive (irritable bowel syndrome, IBS) and healthy controls. Epidemiological and neuroimaging data were collected from participants with UCPPS (n = 52), IBS (n = 39), and healthy sex- and age-matched controls (n = 61). White matter microstructure, measured as fractional anisotropy (FA), was examined by diffusion tensor imaging. Group differences in regional FA positively correlated with pain severity, including segments of the right corticospinal tract and right anterior thalamic radiation. Increased corticospinal FA was specific and sensitive to UCPPS, positively correlated with pain severity, and reflected sensory (not affective) features of pain. Reduced anterior thalamic radiation FA distinguished patients with IBS from those with UCPPS and controls, suggesting greater microstructural divergence from normal tract organization. Findings confirm that regional white matter abnormalities characterize UCPPS and can distinguish between visceral diagnoses, suggesting that regional axonal microstructure is either altered with ongoing pain or predisposes its development.

CHRONIC PAIN (Continued)

Open-label placebo treatment in chronic low back pain: a randomized controlled trial.

Carvalho C[1], Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I.

Pain. **2016 Dec**;157(12):2766-2772. PMCID: PMC5113234.

This randomized controlled trial was performed to investigate whether placebo effects in chronic low back pain could be harnessed ethically by adding open-label placebo (OLP) treatment to treatment as usual (TAU) for 3 weeks. Pain severity was assessed on three 0- to 10-point Numeric Rating Scales, scoring maximum pain, minimum pain, and usual pain, and a composite, primary outcome, total pain score. Our other primary outcome was back-related dysfunction, assessed on the Roland-Morris Disability Questionnaire. In an exploratory follow-up, participants on TAU received placebo pills for 3 additional weeks. We randomized 97 adults reporting persistent low back pain for more than 3 months' duration and diagnosed by a board-certified pain specialist. Eighty-three adults completed the trial. Compared to TAU, OLP elicited greater pain reduction on each of the three 0- to 10-point Numeric Rating Scales and on the 0- to 10-point composite pain scale ($P < 0.001$), with moderate to large effect sizes. Pain reduction on the composite Numeric Rating Scales was 1.5 (95% confidence interval: 1.0-2.0) in the OLP group and 0.2 (-0.3 to 0.8) in the TAU group. Open-label placebo treatment also reduced disability compared to TAU ($P < 0.001$), with a large effect size. Improvement in disability scores was 2.9 (1.7-4.0) in the OLP group and 0.0 (-1.1 to 1.2) in the TAU group. After being switched to OLP, the TAU group showed significant reductions in both pain (1.5, 0.8-2.3) and disability (3.4, 2.2-4.5). Our findings suggest that OLP pills presented in a positive context may be helpful in chronic low back pain.

Is alcohol consumption related to likelihood of reporting chronic widespread pain in people with stable consumption? Results from UK biobank.

Beasley MJ[1], Macfarlane TV, Macfarlane GJ.

Pain. **2016 Nov**;157(11):2552-2560.

Studies have suggested that alcohol consumption is strongly related to reduced reporting of chronic widespread pain (CWP) and level of disability in people with CWP or fibromyalgia. Direction of causality has not been established, that is whether the association is due to people's health influencing their alcohol consumption or vice versa. UK Biobank recruited over 500,000 people aged 40 to 69 years, registered at medical practices nationwide. Participants provided detailed information on health and lifestyle factors including pain and alcohol consumption. Total units consumed per week were calculated for current drinkers. Information was also collected on changes in alcohol consumption and reasons for such changes. Analysis was performed with logistic regression expressed as odds ratios (ORs) with 95% confidence intervals, then adjusted for a large number of potential confounding factors (adjORs). In males who reported drinking the same as 10 years previously, there was a U-shaped relationship between amount drunk and odds of reporting CWP (nondrinkers CWP prevalence 2.4%, 19.1-32.1 units/wk 0.4%, >53.6 units/wk 1.0%; adjORs 2.53 95% confidence intervals [1.78-3.60] vs 1 vs 1.52 [1.05-2.20]). In females, there was a decrease in the proportion reporting CWP up to the modal category of alcohol consumption with no further change in those drinking more (nondrinkers CWP prevalence 3.4%, 6.4-11.2 units/wk 0.7%, >32.1 units/wk 0.7%; adjORs 2.11 [1.67-2.66] vs 1 vs 0.86 [0.54-1.39]). This large study has shown a clear relationship between alcohol consumption and reporting of pain even in people who had not reported changing consumption because of health concerns, after adjustment for potential confounding factors.

CHRONIC PAIN (Continued)

Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study.

Gimbel J[1], Spierings EL, Katz N, Xiang Q, Tzanis E, Finn A.

Pain. **2016 Nov**;157(11):2517-2526. PMCID: PMC5065057.

A buccal film of buprenorphine (BBUP) was evaluated for safety and efficacy in a multicenter, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study in opioid-experienced patients (30 to ≤160 mg/d morphine sulfate equivalent) with moderate to severe chronic low back pain taking around-the-clock opioid analgesics. Patients' opioid doses were tapered to ≤30 mg morphine sulfate equivalent before open-label titration with BBUP (range, 150-900 μg every 12 hours). Patients who responded (received adequate analgesia that was generally well tolerated for 14 days) were randomized to receive buprenorphine (n = 254) or placebo (n = 257) buccal film. The primary efficacy variable was the change from baseline to week 12 of double-blind treatment in mean average daily pain-intensity scores using a rating scale of 0 (no pain) to 10 (worst pain imaginable). In the intent-to-treat population, mean pain scores were 6.7 after opioid taper and declined to 2.8 after the BBUP titration period. After randomization, mean pain scores were lower in the BBUP group than in the placebo group; the difference between groups in the mean change from baseline to week 12 was -0.98 (95% CI, -1.32 to -0.64; P < 0.001). A significantly larger percentage of patients receiving BBUP than placebo had pain reductions ≥30% and ≥50% (P < 0.001 for both). In the double-blind portion of the study, the only adverse event reported more frequently with BBUP than placebo and in ≥5% of patients was vomiting (5.5% vs 2.3%). These findings demonstrate the efficacy and tolerability of BBUP in opioid-experienced patients taking around-the-clock opioid treatment for chronic low back pain.

OTHER RESEARCH OF INTEREST

Effect of concussion and blast exposure on symptoms after military deployment.

Tsao JW[1], Stentz LA[2], Rouhanian M[2], Howard RS[2], Perry BN[2], Haran FJ[2], Pasquina PF[2], Wolde M[2], Taylor CE[2], Lizardo R[2], Liu S[2], Flores E 3rd[2], Creason AH[2], Sher K[2].

Neurology. **2017 Nov 7**;89(19):2010-2016. doi: 10.1212/WNL.0000000000004616. Epub 2017 Oct 13.

OBJECTIVE: To examine whether blast exposure alone and blast-associated concussion result in similar neurologic and mental health symptoms.

METHODS: A 14-item questionnaire was administered to male US Marines on their return from deployment in Iraq and/or Afghanistan.

RESULTS: A total of 2,612 Marines (median age 22 years) completed the survey. Of those, 2,320 (88.9%) reported exposure to ≥1 blast during their current and/or prior deployments. In addition, 1,022 (39.1%) reported ≥1 concussion during the current deployment, and 731 (28.0%) had experienced at least 1 prior lifetime concussion. Marines were more likely to have sustained a concussion during the current deployment if they had a history of 1 (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.2-2.0) or ≥1 (OR 2.3, 95% CI 1.7-3.0) prior concussion. The most common symptoms were trouble sleeping (38.4%), irritability (37.9%), tinnitus (33.8%), and headaches (33.3%). Compared to those experiencing blast exposure without injury, Marines either experiencing a concussion during the current deployment or being moved or injured by a blast had an increased risk of postinjury symptoms.

CONCLUSIONS: There appears to be a continuum of increasing total symptoms from no exposure to blast exposure plus both current deployment concussion and past concussion. Concussion had a greater influence than blast exposure alone on the presence of postdeployment symptoms. A high blast injury score can be used to triage those exposed to explosive blasts for evaluation.

OTHER RESEARCH OF INTEREST (Continued)

Medical contraindications to estrogen and contraceptive use among women veterans.

Judge CP[1], Zhao X[2], Sileanu FE[2], Mor MK[2], Borrero S[3].

Am J Obstet Gynecol. **2017 Oct 27**. pii: S0002-9378(17)31213-9. doi: 10.1016/j.ajog.2017.10.020. [Epub ahead of print]

BACKGROUND: Women veterans have high rates of medical comorbidities and may be particularly vulnerable to adverse health outcomes associated with unintended pregnancy.

OBJECTIVES: The objective of the study was to estimate the prevalence of medical contraindications to estrogen-containing combined hormonal contraception among women veterans of reproductive age and to evaluate the relationship between contraindications and contraceptive use.

STUDY DESIGN: This was a secondary analysis of data from a cross-sectional, telephone-based survey with a national sample of 2302 female veterans, aged 18-45 years, who use the Veterans Administration Healthcare System for primary care. This analysis included women at risk of unintended pregnancy, defined as heterosexually active and not pregnant or trying to conceive and with no history of hysterectomy or infertility. Seven contraindications to combined hormonal contraception were identified using survey data or medical diagnosis codes: hypertension; coronary artery disease; active migraine in women older than 35 years or migraine with aura; smoking in women older than 35 years; and a history of thromboembolism, stroke, or breast cancer. Outcomes were current use of combined hormonal contraception and contraceptive method type (combined hormonal contraception, and other prescription methods, nonprescription methods or no method). Multivariable logistic and multinomial regression were used to assess the relationship between contraindications and combined hormonal contraception use and method type, respectively.

RESULTS: Among 1169 women veterans at risk of unintended pregnancy, 339 (29%) had at least 1 contraindication to combined hormonal contraception. The most prevalent conditions were hypertension (14.9%) and migraine (8.7%). In adjusted analyses, women with contraindications were less likely than women without contraindications to report use of combined hormonal contraception (adjusted odds ratio, 0.54, 95% confidence interval, 0.37-0.79). Relative to use of combined hormonal contraception, women with contraindications were more likely than women without contraindications to use other prescription methods (adjusted odds ratio, 1.74, 95% confidence interval, 1.17-2.60), nonprescription methods (adjusted odds ratio, 1.96, 95% confidence interval, 1.19-3.22), and no method (adjusted odds ratio, 2.29, 95% confidence interval, 1.35-3.89).

CONCLUSION: Women veterans at risk of unintended pregnancy have a high burden of medical contraindications to estrogen. Women with contraindications were less likely to use combined hormonal contraceptive methods but were more likely to use no method, suggesting an unmet need for contraception in this medically vulnerable population.

2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria.

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, Mease PJ, Russell AS, Russell IJ, Walitt B.

Semin Arthritis Rheum. **2016 Dec**;46(3):319-329. doi: 10.1016/j.semarthrit.2016.08.012. Epub 2016 Aug 30.

OBJECTIVES: The provisional criteria of the American College of Rheumatology (ACR) 2010 and the 2011 self-report modification for survey and clinical research are widely used for fibromyalgia diagnosis. To determine the validity, usefulness, potential problems, and modifications required for the criteria, we assessed multiple research reports published in 2010-2016 in order to provide a 2016 update to the criteria.

METHODS: We reviewed 14 validation studies that compared 2010/2011 criteria with ACR 1990 classification and clinical criteria, as well as epidemiology, clinical, and databank studies that addressed important criteria-level variables. Based on definitional differences between 1990 and 2010/2011 criteria, we interpreted 85% sensitivity and 90% specificity as excellent agreement.

RESULTS: Against 1990 and clinical criteria, the median sensitivity and specificity of the 2010/2011 criteria were 86% and 90%, respectively. The 2010/2011 criteria led to misclassification when applied to regional pain syndromes, but when a modified widespread pain criterion (the "generalized pain criterion") was added misclassification was eliminated. Based on the above data and clinic usage data, we developed a (2016) revision to the 2010/2011 fibromyalgia criteria. Fibromyalgia may now be diagnosed in adults when all of the following criteria are met: CONCLUSIONS: The fibromyalgia criteria have good sensitivity and specificity. This revision combines physician and questionnaire criteria, minimizes misclassification of regional pain disorders, and eliminates the previously confusing recommendation regarding diagnostic exclusions. The physician-based criteria are valid for individual patient diagnosis. The self-report version of the criteria is not valid for clinical diagnosis in individual patients but is valid for research studies. These changes allow the criteria to function as diagnostic criteria, while still being useful for classification.

OTHER RESEARCH OF INTEREST (Continued)

Functional Brain Imaging Updates on the Horizon.

Abbasi J.

JAMA. **2017 Nov 14**;318(18):1750. doi: 10.1001/jama.2017.17314. PMID: 29136425.

View full text in JAMA.

Two teams of researchers are poised to bring new functional brain imaging technologies to the clinic.

First, within a few years, physicians could have a way to monitor brain function at the bedside of hospitalized infants, something that is not currently possible with large functional magnetic resonance imaging (fMRI) machines.

European researchers have developed a portable brain scanning technology called functional ultrasound imaging (fUSI). The fUSI system employs a flexible, noninvasive head mount and combines video-electroencephalographic recording with ultrafast Doppler (UfD) imaging of brain microvasculature.

The researchers previously developed the UfD technology, which produces up to 10 000 images per second, compared with 50 images per second in conventional ultrasound, enabling detection of small vessels or low blood flow in neonates.

The variations in blood volume during the recordings are correlated with neuronal activity and could provide information on neonatal brain function in conditions such as hemodynamic failure, congenital heart defects, and sepsis, said Olivier Baud, MD, PhD, who co-led the development of fUSI while working at Robert Debré Children's Hospital in Paris.

In a proof-of-concept study in *Science Translational Medicine*, the investigators demonstrated fUSI's ability to visualize cerebral blood volume changes in response to changes in brain activity during sleep states and seizures in neonates. Further study is needed on the safety of brain ultrasound scanning over long exposure times, the researchers said.

Also on the horizon is a next-generation MRI scanner that can zoom in on brain regions as small as a poppy seed—a 20-fold increase in spatial resolution compared with current machines.

Researchers at the University of California, Berkeley, will build a prototype machine over the next 2 years with a recently announced $13.43 million Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative grant from the National Institutes of Health.

The new technology, dubbed MR Corticography (MRCoG), will advance fMRI and diffusion imaging of cortical layers delineating distinct populations of neurons.

"Each cortical layer is a part of specific circuitry," explained principal investigator David Feinberg, MD, PhD, adjunct professor of neuroscience at UC Berkeley and president of Advanced MRI Technologies. "Therefore, the new scanner is designed to identify neuronal circuitry abnormalities for earlier and more specific diagnosis of abnormal brain conditions such as epilepsy, autism spectrum disorders, Alzheimer disease, chronic pain, and psychiatric disorders."

The gain in resolution comes from a combination of innovations including a larger number of smaller receiver coils, higher-performance gradient coils, faster imaging pulse sequences, and reduced noise in image reconstruction.

"By achieving a resolution that approaches the size of fundamental organizational units of the human cortex, we will be able to study the cortical neural circuitry defining the communications between cortical layers and columns," Feinberg said. "This will help close the gap between our understanding of neural activity at the cellular levels and human behavior and cognition."

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