

## GULF WAR ILLNESS

### [The Association Between Toxic Exposures and Chronic Multisymptom Illness in Veterans of the Wars of Iraq and Afghanistan.](#)

DeBeer BB, Davidson D, Meyer EC, Kimbrel NA, Gulliver SB, Morissette SB.

J Occup Environ Med. 2017 Jan;59(1):54-60. doi: 10.1097/JOM.0000000000000922.

**OBJECTIVE:** The purpose of this study was to determine if post-9/11 veterans deployed to the Iraq and Afghanistan conflicts experienced toxic exposures and whether they are related to symptoms of chronic multisymptom illness (CMI).

**METHODS:** Data from 224 post-9/11 veterans who self-reported exposure to hazards in theater were analyzed using hierarchical regression.

**RESULTS:** Of the sample, 97.2% endorsed experiencing one or more potentially toxic exposure. In a regression model, toxic exposures and CMI symptoms were significantly associated above and beyond covariates. Follow-up analyses revealed that pesticide exposures, but not smoke inhalation was associated with CMI symptoms.

**CONCLUSIONS:** These findings suggest that toxic exposures were common among military personnel deployed to the most recent conflicts, and appear to be associated with CMI symptoms. Additional research on the impact of toxic exposures on returning Iraq and Afghanistan Veterans' health is needed.

## CHRONIC FATIGUE SYNDROME

### [Heterogeneity in chronic fatigue syndrome - empirically defined subgroups from the PACE trial.](#)

Williams TE, Chalder T, Sharpe M, White PD.

Psychol Med. 2017 Jan 23:1-12. doi: 10.1017/S0033291716003615. [Epub ahead of print]

**BACKGROUND:** Chronic fatigue syndrome is likely to be a heterogeneous condition. Previous studies have empirically defined subgroups using combinations of clinical and biological variables. We aimed to explore the heterogeneity of chronic fatigue syndrome.

**METHOD:** We used baseline data from the PACE trial, which included 640 participants with chronic fatigue syndrome. Variable reduction, using a combination of clinical knowledge and principal component analyses, produced a final dataset of 26 variables for 541 patients. Latent class analysis was then used to empirically define subgroups.

**RESULTS:** The most statistically significant and clinically recognizable model comprised five subgroups. The largest, 'core' subgroup (33% of participants), had relatively low scores across all domains and good self-efficacy. A further three subgroups were defined by: the presence of mood disorders (21%); the presence of features of other functional somatic syndromes (such as fibromyalgia or irritable bowel syndrome) (21%); or by many symptoms - a group which combined features of both of the above (14%). The smallest 'avoidant-inactive' subgroup was characterized by physical inactivity, belief that symptoms were entirely physical in nature, and fear that they indicated harm (11%). Differences in the severity of fatigue and disability provided some discriminative validation of the subgroups.

**CONCLUSIONS:** In addition to providing further evidence for the heterogeneity of chronic fatigue syndrome, the subgroups identified may aid future research into the important aetiological factors of specific subtypes of chronic fatigue syndrome and the development of more personalized treatment approaches.

**CHRONIC FATIGUE SYNDROME (Continued)**[Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: An exploratory pilot study.](#)

Windthorst P, Mazurak N, Kuske M, Hipp A, Giel KE, Enck P, Nieß A, Zipfel S, Teufel M.

J Psychosom Res. 2017 Feb;93:6-13. doi: 10.1016/j.jpsychores.2016.11.014.

**OBJECTIVE:** Chronic fatigue syndrome (CFS) is characterised by persistent fatigue, exhaustion, and several physical complaints. Research has shown cognitive behavioural therapy (CBT) and graded exercise training (GET) to be the most effective treatments. In a first step we aimed to assess the efficacy of heart rate variability biofeedback therapy (HRV-BF) as a treatment method comprising cognitive and behavioural strategies and GET in the pilot trial. In a second step we aimed to compare both interventions with regard to specific parameters.

**METHODS:** The study was conducted in an outpatient treatment setting. A total of 28 women with CFS (50.3±9.3years) were randomly assigned to receive either eight sessions of HRV-BF or GET. The primary outcome was fatigue severity. Secondary outcomes were mental and physical quality of life and depression. Data were collected before and after the intervention as well as at a 5-month follow-up.

**RESULTS:** General fatigue improved significantly after both HRV-BF and GET. Specific cognitive components of fatigue, mental quality of life, and depression improved significantly after HRV-BF only. Physical quality of life improved significantly after GET. There were significant differences between groups regarding mental quality of life and depression favouring HRV-BF.

**CONCLUSION:** Both interventions reduce fatigue. HRV-BF seems to have additional effects on components of mental health, including depression, whereas GET seems to emphasise components of physical health. These data offer implications for further research on combining HRV-BF and GET in patients with CFS.

[Telephone-administered versus live group cognitive behavioral stress management for adults with CFS.](#)

Hall DL, Lattie EG, Milrad SF, Czaja S, Fletcher MA, Klimas N, Perdomo D, Antoni MH.

J Psychosom Res. 2017 Feb;93:41-47. doi: 10.1016/j.jpsychores.2016.12.004.

**OBJECTIVE:** Chronic fatigue syndrome (CFS) symptoms have been shown to be exacerbated by stress and ameliorated by group-based psychosocial interventions such as cognitive behavioral stress management (CBSM). Still, patients may have difficulty attending face-to-face groups. This study compared the effects of a telephone-delivered (T-CBSM) vs a live (L-CBSM) group on perceived stress and symptomology in adults with CFS.

**METHODS:** Intervention data from 100 patients with CFS (mean age 50years; 90% female) participating in T-CBSM (N=56) or L-CBSM (N=44) in previously conducted randomized clinical trials were obtained. Perceived Stress Scale (PSS) and the Centers for Disease Control and Prevention symptom checklist scores were compared with repeated measures analyses of variance in adjusted and unadjusted analyses.

**RESULTS:** Participants across groups showed no differences in most demographic and illness variables at study entry and had similar session attendance. Both conditions showed significant reductions in PSS scores, with L-CBSM showing a large effect (partial  $\epsilon^2=0.16$ ) and T-CBSM a medium effect (partial  $\epsilon^2=0.095$ ). For CFS symptom frequency and severity scores, L-CBSM reported large effect size improvements (partial  $\epsilon^2=0.19-0.23$ ), while T-CBSM showed no significant changes over time.

**CONCLUSIONS:** Two different formats for delivering group-based CBSM-live and telephone-showed reductions in perceived stress among patients with CFS. However, only the live format was associated with physical symptom improvements, with specific effects on post-exertional malaise, chills, fever, and restful sleep. The added value of the live group format is discussed, along with implications for future technology-facilitated group interventions in this population.

## CHRONIC FATIGUE SYNDROME (Continued)

### [Chronic Fatigue Syndrome: Cognitive, Behavioural and Emotional Processing Vulnerability Factors.](#)

Brooks SK, Chalder T, Rimes KA.

Behav Cogn Psychother. 2017 Jan 18:1-14. doi: 10.1017/S1352465816000631. [Epub ahead of print]

**BACKGROUND:** Cognitive-behavioural models of chronic fatigue syndrome (CFS) suggest that personality factors such as perfectionism and high moral standards may contribute to the development of CFS.

**AIMS:** To investigate cognitive, behavioural and emotional processing risk factors for CFS.

**METHOD:** CFS patients (n = 67) at a UK specialist clinic completed questionnaires about psychological characteristics both currently and retrospectively (6 months pre-CFS onset). Responses were compared with those of healthy individuals (n = 73) who rated their current characteristics. Forty-four relatives retrospectively rated the pre-morbid psychological characteristics of the CFS participants.

**RESULTS:** CFS patients showed similar levels of current perfectionism to controls, though higher pre-morbid perfectionism. CFS patients showed greater self-sacrificial beliefs and more unhelpful beliefs about experiencing and expressing negative emotions, both currently but more markedly prior to onset. In the 6 months pre-illness onset, CFS patients showed more disruption to their primary goal and greater general stress than controls. Ratings of pre-morbid psychological characteristics by relatives were consistent with patients' self-reports. The extent of overinvestment in one goal was significantly associated with fatigue.

**CONCLUSIONS:** Perfectionism, self-sacrificial tendencies, unhelpful beliefs about emotions, and perceived stress may be present to a greater extent pre-morbidly in CFS patients compared with healthy individuals.

## HEADACHE MIGRAINE

### [Migraine Headache and Long Term Cardiovascular Outcomes: An extended follow-up of the Women's Ischemia Syndrome Evaluation.](#)

Rambarat CA, Elgendy IY, Johnson BD, Reis SE, Thompson DV, Sharaf BL, Bittner V, Sopko G, Bairey Merz CN, Pepine CJ, Ahmed B.

Am J Med. 2017 Jan 18. pii: S0002-9343(17)30031-1. doi:

**BACKGROUND:** The association between migraine headache and cardiovascular events has been inconsistent. This study determines the long-term risk of cardiovascular events among women with and without a history of migraine headache who were under evaluation for suspected myocardial ischemia in the Women's Ischemia Syndrome Evaluation (WISE).

**METHODS:** The WISE is a National Heart, Lung and Blood Institute sponsored prospective, multicenter study which aims to improve myocardial ischemia evaluation in women. A total of 936 women presenting with symptoms of myocardial ischemia underwent structured data collection and coronary angiography. Information pertaining to migraine headache was available in 917 women. All-cause mortality data were available on all women for a median of 9.5 years and non-fatal cardiovascular event data were available on 888 women for a median of 6.5 years.

**RESULTS:** A total of 224 (24.4%) women reported a history of migraine headache. Compared with women who did not report a history of migraine headache, women with a history of migraine headache had an increased adjusted risk of cardiovascular event (cardiovascular death, non-fatal myocardial infarction, heart failure or stroke) (HR 1.83 CI 1.22-2.75) at a median follow up of 6.5 years. This result was driven mainly by a two-fold increase in the risk of stroke (HR 2.33 CI 1.16-4.68).

**CONCLUSION:** Among women being evaluated for ischemic heart disease, those reporting a history of migraine headache had increased risk of future cardiovascular events on long-term follow up. This risk was primarily driven by a more than two-fold increase in the risk of stroke.

## HEADACHE MIGRAINE (Continued)

### [Neuroendocrine signaling modulates specific neural networks relevant to migraine.](#)

Martins-Oliveira M, Akerman S, Holland PR, Hoffmann JR, Tavares I, Goadsby PJ.

Neurobiol Dis. 2017 Jan 17. pii: S0969-9961(17)30014-1. doi: 10.1016/j.nbd.2017.01.005. [Epub ahead of print]

Migraine is a disabling brain disorder involving abnormal trigeminovascular activation and sensitization. Fasting or skipping meals is considered a migraine trigger and altered fasting glucose and insulin levels have been observed in migraineurs. Therefore peptides involved in appetite and glucose regulation including insulin, glucagon and leptin could potentially influence migraine neurobiology. We aimed to determine the effect of insulin ( $10\text{U}\cdot\text{kg}^{-1}$ ), glucagon ( $100\mu\text{g}\cdot 200\mu\text{l}^{-1}$ ) and leptin ( $0.3, 1$  and  $3\text{mg}\cdot\text{kg}^{-1}$ ) signaling on trigeminovascular nociceptive processing at the level of the trigeminocervical-complex and hypothalamus. Male rats were anesthetized and prepared for craniovascular stimulation. In vivo electrophysiology was used to determine changes in trigeminocervical neuronal responses to dural electrical stimulation, and phosphorylated extracellular signal-regulated kinases 1 and 2 (pERK1/2) immunohistochemistry to determine trigeminocervical and hypothalamic neural activity; both in response to intravenous administration of insulin, glucagon, leptin or vehicle control in combination with blood glucose analysis. Blood glucose levels were significantly decreased by insulin ( $p<0.001$ ) and leptin ( $p<0.01$ ) whereas glucagon had the opposite effect ( $p<0.001$ ). Dural-evoked neuronal firing in the trigeminocervical-complex was significantly inhibited by insulin ( $p<0.001$ ), glucagon ( $p<0.05$ ) and leptin ( $p<0.01$ ). Trigeminocervical-complex pERK1/2 cell expression was significantly decreased by insulin and leptin (both  $p<0.001$ ), and increased by glucagon ( $p<0.001$ ), when compared to vehicle control. However, only leptin affected pERK1/2 expression in the hypothalamus, significantly decreasing pERK1/2 immunoreactive cell expression in the arcuate nucleus ( $p<0.05$ ). These findings demonstrate that insulin, glucagon and leptin can alter the transmission of trigeminal nociceptive inputs. A potential neurobiological link between migraine and impaired metabolic homeostasis may occur through disturbed glucose regulation and a transient hypothalamic dysfunction.

### [Neuropsychological assessment in migraine patients: a descriptive review on cognitive implications.](#)

Foti M, Buono VL, Corallo F, Palmeri R, Bramanti P, Marino S.

Neurol Sci. 2017 Jan 18. doi: 10.1007/s10072-017-2814-z. [Epub ahead of print]

Review.

Migraine is considered a disabling disorder with highly prevalence in population. Recent studies report that migraine patients have a cognitive decline associated to structural brain alterations. We search on PubMed and Web of Science databases and screening references of included studies and review articles for additional citations. From 519 studies identified, only 16 met the inclusion criteria. All studies were conducted on 1479 migraineurs (190 non-migraine headache and 11,978 controls subject) and examined the association between migraine and cognitive impairment. The results are discordant. Indeed, while cognitive deficits during the attack of migraine are now recognized, only few studies confirmed the presence of cognitive impairment in migraine patients. Given the prevalence of migraine in the population (especially among women), and the early age of the population, an association between migraine and cognitive impairment could have substantial public health implications. Future studies should determine if specific migraine characteristics, for example, attack frequency, may impact the association between migraine and cognitive decline.

## HEADACHE MIGRAINE (Continued)

### [Cortico-Cortical Connections of Primary Sensory Areas and Associated Symptoms in Migraine.](#)

Hodkinson DJ, Veggeberg R, Kucyi A, van Dijk KR, Wilcox SL, Scrivani SJ, Burstein R, Becerra L, Borsook D.

eNeuro. 2017 Jan 17;3(6). pii: ENEURO.0163-16.2016. doi: 10.1523/ENEURO.0163-16.2016.

Migraine is a recurring, episodic neurological disorder characterized by headache, nausea, vomiting, and sensory disturbances. These events are thought to arise from the activation and sensitization of neurons along the trigemino-vascular pathway. From animal studies, it is known that thalamocortical projections play an important role in the transmission of nociceptive signals from the meninges to the cortex. However, little is currently known about the potential involvement of cortico-cortical feedback projections from higher-order multisensory areas and/or feedforward projections from principle primary sensory areas or subcortical structures. In a large cohort of human migraine patients ( $N = 40$ ) and matched healthy control subjects ( $N = 40$ ), we used resting-state intrinsic functional connectivity to examine the cortical networks associated with the three main sensory perceptual modalities of vision, audition, and somatosensation. Specifically, we sought to explore the complexity of the sensory networks as they converge and become functionally coupled in multimodal systems. We also compared self-reported retrospective migraine symptoms in the same patients, examining the prevalence of sensory symptoms across the different phases of the migraine cycle. Our results show widespread and persistent disturbances in the perceptions of multiple sensory modalities. Consistent with this observation, we discovered that primary sensory areas maintain local functional connectivity but express impaired long-range connections to higher-order association areas (including regions of the default mode and salience network). We speculate that cortico-cortical interactions are necessary for the integration of information within and across the sensory modalities and, thus, could play an important role in the initiation of migraine and/or the development of its associated symptoms.

## CHRONIC PAIN

### [Pain has an element of blank - a biobehavioral approach to chronicity.](#)

Flor H.

Pain. 2017 Jan 18. doi: 10.1097/j.pain.0000000000000850. [Epub ahead of print] PMID: 28114184

The development of acute to chronic pain is characterized by a shift from nociceptive brain circuits to those involved in emotion, motivation, cognition and learning. Psychological, psychosocial, genetic and neurobiological determinants of these evolving brain circuits are discussed and it is suggested that different concepts of chronicity may have a common psychobiological basis. The analysis of these chronicity factors leads to the identification of psychobiological mechanisms of chronicity and may change the classification of pain syndromes from a mainly descriptive to a mechanistic basis. Both, chronicity and resilience factors must be examined and subgroups of patients with common characteristics need to be defined. Treatments must target these shifts in brain circuits.

**CHRONIC PAIN (Continued)**[Promoted Interaction of C/EBP \$\alpha\$  with Demethylated Cxcr3 Gene Promoter Contributes to Neuropathic Pain in Mice.](#)

Jiang BC, He LN, Wu XB, Shi H, Zhang WW, Zhang ZJ, Cao DL, Li CH, Gu J, Gao YJ.

J Neurosci. 2017 Jan 18;37(3):685-700. doi: 10.1523/JNEUROSCI.2262-16.2017.

DNA methylation has been implicated in the pathogenesis of chronic pain. However, the specific genes regulated by DNA methylation under neuropathic pain condition remain largely unknown. Here we investigated how chemokine receptor CXCR3 is regulated by DNA methylation and how it contributes to neuropathic pain induced by spinal nerve ligation (SNL) in mice. SNL increased Cxcr3 mRNA and protein expression in the neurons of the spinal cord. Meanwhile, the CpG (5'-cytosine-phosphate-guanine-3') island in the Cxcr3 gene promoter region was demethylated, and the expression of DNA methyltransferase 3b (DNMT3b) was decreased. SNL also increased the binding of CCAAT (cytidine-cytidine-adenosine-adenosine-thymidine)/enhancer binding protein  $\alpha$  (C/EBP $\alpha$ ) with Cxcr3 promoter and decreased the binding of DNMT3b with Cxcr3 promoter in the spinal cord. C/EBP $\alpha$  expression was increased in spinal neurons after SNL, and inhibition of C/EBP $\alpha$  by intrathecal small interfering RNA attenuated SNL-induced pain hypersensitivity and reduced Cxcr3 expression. Furthermore, SNL-induced mechanical allodynia and heat hyperalgesia were markedly reduced in Cxcr3<sup>-/-</sup> mice. Spinal inhibition of Cxcr3 by shRNA or CXCR3 antagonist also attenuated established neuropathic pain. Moreover, CXCL10, the ligand of CXCR3, was increased in spinal neurons and astrocytes after SNL. Superfusing spinal cord slices with CXCL10 enhanced spontaneous EPSCs and potentiated NMDA-induced and AMPA-induced currents of lamina II neurons. Finally, intrathecal injection of CXCL10 induced CXCR3-dependent pain hypersensitivity in naive mice. Collectively, our results demonstrated that CXCR3, increased by DNA demethylation and the enhanced interaction with C/EBP $\alpha$ , can be activated by CXCL10 to facilitate excitatory synaptic transmission and contribute to the maintenance of neuropathic pain.

**SIGNIFICANCE STATEMENT:** Peripheral nerve injury induces changes of gene expression in the spinal cord that may contribute to the pathogenesis of neuropathic pain. CXCR3 is a chemokine receptor. Whether it is involved in neuropathic pain and how it is regulated after nerve injury remain largely unknown. Our study demonstrates that spinal nerve ligation downregulates the expression of DNMT3b, which may cause demethylation of Cxcr3 gene promoter and facilitate the binding of CCAAT/enhancer binding protein  $\alpha$  with Cxcr3 promoter and further increase CXCR3 expression in spinal neurons. The upregulated CXCR3 may contribute to neuropathic pain by facilitating central sensitization. Our study reveals an epigenetic mechanism underlying CXCR3 expression and also suggests that targeting the expression or activation of CXCR3 signaling may offer new therapeutics for neuropathic pain.

## CHRONIC PAIN (Continued)

### [Compensatory Activation of Cannabinoid CB2 Receptor Inhibition of GABA Release in the Rostral Ventromedial Medulla in Inflammatory Pain.](#)

Li MH, Suchland KL, Ingram SL.

J Neurosci. 2017 Jan 18;37(3):626-636. doi: 10.1523/JNEUROSCI.1310-16.2017.

The rostral ventromedial medulla (RVM) is a relay in the descending pain modulatory system and an important site of endocannabinoid modulation of pain. Endocannabinoids inhibit GABA release in the RVM, but it is not known whether this effect persists in chronic pain states. In the present studies, persistent inflammation induced by complete Freund's adjuvant (CFA) increased GABAergic miniature IPSCs (mIPSCs). Endocannabinoid activation of cannabinoid (CB1) receptors known to inhibit presynaptic GABA release was significantly reduced in the RVM of CFA-treated rats compared with naive rats. The reduction in CFA-treated rats correlated with decreased CB1 receptor protein expression and function in the RVM. Paradoxically, the nonselective CB1/CB2 receptor agonist WIN55212 inhibited GABAergic mIPSCs in both naive and CFA-treated rats. However, WIN55212 inhibition was reversed by the CB1 receptor antagonist rimonabant in naive rats but not in CFA-treated rats. WIN55212-mediated inhibition in CFA-treated rats was blocked by the CB2 receptor-selective antagonist SR144528, indicating that CB2 receptor function in the RVM is increased during persistent inflammation. Consistent with these results, CB2 receptor agonists AM1241 and GW405833 inhibited GABAergic mIPSC frequency only in CFA-treated rats, and the inhibition was reversed with SR144528. When administered alone, SR144528 and another CB2 receptor-selective antagonist AM630 increased mIPSC frequency in the RVM of CFA-treated rats, indicating that CB2 receptors are tonically activated by endocannabinoids. Our data provide evidence that CB2 receptor function emerges in the RVM in persistent inflammation and that selective CB2 receptor agonists may be useful for treatment of persistent inflammatory pain.

**SIGNIFICANCE STATEMENT:** These studies demonstrate that endocannabinoid signaling to CB1 and CB2 receptors in adult rostral ventromedial medulla is altered in persistent inflammation. The emergence of CB2 receptor function in the rostral ventromedial medulla provides additional rationale for the development of CB2 receptor-selective agonists as useful therapeutics for chronic inflammatory pain.

### [Effectiveness of High Intensity Laser Therapy for Reduction of Pain in Knee Osteoarthritis.](#)

Angelova A, Ilieva EM.

Pain Res Manag. 2016;2016:9163618. doi: 10.1155/2016/9163618.

*Introduction.* Osteoarthritis is the most common type of arthritis. It is the main cause of chronic musculoskeletal pain and disability among the elderly population.

*Aim.* This is a pilot, randomized clinical study about the effect of high intensity laser therapy in patients with osteoarthritis of the knee (OA of the knee).

*Material and Method.* 72 patients (aged between 39 and 83 years) with (clinically and radiographically proved) OA of the knee were included in the study. They were randomized in two groups: therapeutic (test) one ( $n = 37$ ,  $65,11 \pm 1,40$  (mean  $\pm$  SD) years old; patients were treated with HILT) and control group ( $n = 35$ ,  $64,71 \pm 1,98$ ; patients receive sham laser). Both groups had seven sessions of treatment. VAS and dolorimetry were used for assessment of pain before and after the therapy. Pedobarometric analysis (static and dynamic) was used to assess comparatively the contact surface area and maximum pressure under the heel.

*Results.* Pain levels measured by VAS and dolorimetry decreased significantly in the therapeutic group after seven days of treatment ( $p < 0,001$ ).

*Conclusion.* The results after seven days of treatment show more intensive and cumulative effect after the application of high intensity laser therapy in comparison to sham laser. This is the reason why HILT can be a method of choice in the treatment of gonarthrosis.

**CHRONIC PAIN (Continued)**[Cost-effectiveness of using a motion-sensor biofeedback treatment approach for the management of sub-acute or chronic low back pain: economic evaluation alongside a randomised trial.](#)

Haines T, Bowles KA.

BMC Musculoskelet Disord. 2017 Jan 17;18(1):18. doi: 10.1186/s12891-016-1371-6.

**BACKGROUND:** Low back pain is a common and costly condition internationally. There is high need to identify effective and economically efficient means for managing this problem. This study aimed to explore the cost-effectiveness of a novel motion-sensor biofeedback treatment approach in addition to guidelines-based care compared to guidelines-based care alone, from a societal perspective over a 12 month time horizon.

**METHOD:** This was an incremental cost-effectiveness analysis conducted concurrently with a pilot, cluster randomized controlled trial. Health care resource use was collected using daily diaries and patient-self report at 3, 6 and 12 month follow-up assessments. Productivity was measured using industry classifications and participant self-reporting of ability to do their normal work with their present pain. Clinical effect was measured using the Patient Global Impression of Change measured at the 12 month follow-up assessment. Data were compared between groups using linear regression clustered by recruitment site. Bootstrap resampling was used to generate a visual representation of the 95% confidence interval for the incremental cost-effectiveness estimate. Two, one-way sensitivity analyses were undertaken to examine the robustness of findings to key assumptions.

**RESULT:** There were n = 38 participants in the intervention group who completed the 12 month assessment and n = 45 in the control. The intervention group had greater use of trial-related medical and therapy resources [\$477 per participant (95% CI: \$447, \$508)], but lower use of non-trial medical and therapy resources [\$-53 per participant (95% CI: \$-105, \$-0)], and a greater improvement in productivity [\$-5123 per participant (95% CI: \$-10,174, \$-72)]. Overall, the intervention dominated with a saving of \$478,100 and an additional 41 participants self-rating as being very or much improved compared to the control. There was >99% confidence in this finding of dominance in both the primary and sensitivity analyses.

**CONCLUSIONS:** The motion-sensor biofeedback treatment approach in addition to guidelines-based care appears to be both more clinically effective and economically efficient than guidelines-based care alone. This approach appears to be a viable means to manage low back pain and further research in this area should be a priority.

## CHRONIC PAIN (Continued)

[Evidence Brief: The Comparative Effectiveness of Selected Complementary and Integrative Health \(CIH\) Interventions for Preventing or Reducing Opioid Use in Adults with Chronic Neck, Low Back, and Large Joint Pain.](#)

Peterson K, Anderson J, Ferguson L, Mackey K.

**VA Evidence-based Synthesis Program Evidence Briefs** [Internet]. Washington (DC): Department of Veterans Affairs (US); 2011-. No abstract available. 2016 Apr.

Over the past 2 decades, there has been a dramatic increase in opioid-related overdose deaths, dependence, and misuse. As a result, there is intense interest in non-opioid alternatives for treating chronic pain. Select Complementary and Integrative Health (CIH) interventions may be a reasonable non-opioid treatment option in general, if they can improve pain at a magnitude comparable to opioids, but without serious side effects. Whether CIH interventions can reduce chronic opioid use is of great interest in the fight against the opioid epidemic.

The evidence base regarding the effectiveness of select CIH interventions for reducing opioid use is extremely limited. No study has evaluated the effectiveness of select CIH interventions for reducing new opioid use, stopping opioids entirely, or for reducing opioid use below any particular morphine equivalent dose (MED) threshold. Compared to sham, in patients already using a dosage below 80 mg MED, there is low-strength evidence that certain electro-acupuncture modalities can reduce opioid dose after 6 to 10 weeks of treatment. This was found both in a group of Australian patients with various forms of chronic pain undergoing a planned opioid tapering and in a group of Veterans with advanced knee osteoarthritis taking opioids for an unknown duration. But these effects were not sustained 5-9 months following acupuncture discontinuation. Single studies of massage, meditation, and yoga provided insufficient evidence to draw conclusions about their effects on opioid dose because (1) they lacked details about opioid type, dose, and frequency and (2) relied on self-assessments from unblinded patients, with no effort to match the intervention to a sham treatment group, which could have led to more favorable assessments in the experimental groups. We found no studies that evaluated the impact of tai chi or classic acupuncture on opioid use.

Additional research is needed to better understand the effectiveness of select CIH interventions for reducing opioid use in Veterans. To best remedy key limitations of current evidence, future research should seek to: (1) evaluate the most clinically relevant outcomes of reducing new use, stopping opioids entirely, and/or reducing opioid use below relevant MED threshold(s) using suggested measurement methods, (2) simultaneously measure a complete set of key outcomes, including impact on pain, pain-related function, quality of life, and harms, including potential consequences of reducing opioid use, (3) clarify whether the effectiveness of CIH varies depending on the timing of their integration, and (4) identify particular subpopulations that are more or less likely to benefit from CIH to reduce opioid use and whether variation in benefit varies by CIH type.