

## GULF WAR ILLNESS

### [Increased Risk of Chronic Multisymptom Illness in Spouses of Gulf War Era Veterans.](#)

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Mil Med. 2017 May;182(5):e1648-e1656. doi: 10.7205/MILMED-D-16-00194. PMID: 29087907.

**OBJECTIVE:** In 1995, the Centers for Disease Control and Prevention defined chronic multisymptom illness (CMI), a symptom complex in deployed veterans (DVs) of the 1991 Gulf War 1. The specific aim of this work is to determine the prevalence of CMI in spouses of DV and nondeployed veterans (NDVs) and whether veteran CMI is associated with spouse CMI, and to describe the physical and psychological profile of spouses with CMI.

**MATERIALS AND METHODS:** To determine whether veteran CMI was associated with CMI in their spouses, we used retrospective data from the "National Health Survey of Gulf War Veterans and Their Families." Cross-sectional data were collected from spouses of veterans enrolled in the study, including those of 482 DVs and 532 NDVs who participated in an in-person examination between 1999 and 2001. In addition to a physical examination, this study evaluated health-related quality of life (Medical Outcomes Study Short-Form 36, SF-36), psychological symptoms, and post-traumatic stress disorder (PTSD) status, and measured a variety of common laboratory tests. Statistical analyses included Fisher's Exact Test (or Mantel-Haenszel  $\chi^2$  test for linear trend) as well as odds ratios (ODs) and 95% confidence intervals (CIs) for categorical data. For continuous outcomes, two-sample t-tests were used to compare mean responses among spouses of DV and NDV with and without CMI, and between spouses of DV and NDV with CMI only. Logistic or linear regression models were developed for multiple-covariate analysis to assess if any of the associations we found in the unadjusted analyses would change. The project was approved by the Hines Cooperative Studies Program Human Rights Committee, the Institutional Review Boards at each participating site, and the Brockton VAMC.

**RESULTS:** The prevalence of CMI in spouses was 19.5% (DV) and 17.3% (NDV) (odds ratio [OR]: 1.16; 95% confidence interval [CI]: 0.84, 1.59). Spouses were more likely to have CMI if their veteran partner had CMI (OR: 1.49; 95% CI: 1.01, 2.19) or PTSD (OR: 1.84; 95% CI: 1.01, 3.37). Deployment was not a predictor of CMI. Spouses with CMI reported poorer SF-36 physical and mental component scores; worse symptoms of depression, anxiety, and post-traumatic stress; and a higher percentage had probable PTSD, more nonroutine clinic visits, more hospitalization, more prescription medications, and more psychotropic medication use compared with spouses without CMI regardless of the deployment status of their veteran spouses.

**CONCLUSION:** Spouses of veterans with CMI report worse physical and mental functioning than spouses of veterans without CMI, regardless of the veteran's deployment status. Strengths of the study include that all participants were selected independently of veteran medical or psychiatric illness, and all underwent comprehensive health assessments. Weaknesses of the study include that data were not collected blindly, and that we made minor modifications of the Centers for Disease Control and Prevention diagnosis, such as defining fatigue and musculoskeletal pain more restrictively. The impact of veteran CMI on their spouse's health is likely to be significant in terms of medical cost and morbidity. Efforts to reduce the impact of CMI in the future should include identifying soldiers who are more vulnerable, such as those with prior GWI or PTSD.

## GULF WAR ILLNESS (Continued)

### [Evidence of Objective Memory Impairments in Deployed Gulf War Veterans With Subjective Memory Complaints.](#)

[Chao LL](#)<sup>1</sup>.

Mil Med. **2017 May**;182(5):e1625-e1631. doi: 10.7205/MILMED-D-16-00309. PMID: 29087904.

**INTRODUCTION:** Despite the fact that many veterans returned from the 1991 Gulf War (GW) with complaints of memory difficulties, most neuropsychological studies to date have found little evidence of a correspondence between subjective and objective measures of cognitive function in GW veterans. However, if GW veterans complain about memory problems, it is likely that they experience memory problems in their daily lives. In this respect, it is notable that the past studies that have investigated the relationship between subjective and objective measures of cognitive function in GW veterans used composite measures to quantify subjective complaints and batteries of neuropsychological tests that assessed multiple domains to objectively measure cognitive function. The study's focus on memory was motivated by the suggestive evidence that subjective memory complaint may be a harbinger of further cognitive decline and increased risk for dementia.

**MATERIALS AND METHODS:** This study examined the association between subjective memory complaint (probed with single question: "Do you have difficulty remembering things?") and performance on a single objective test of verbal learning and memory (i.e., California Verbal Learning Test, CVLT-II) in a sample of 428 deployed GW veterans.

**RESULTS:** GW veterans who endorsed memory difficulties performed more poorly on CVLT-II measures of total learning, retention, and delayed recall than GW veterans without subjective memory complaints ( $p < 0.001$ ), even after accounting for demographic (e.g., age, sex, education) and clinical variables (e.g., diagnoses of current post-traumatic stress disorder [PTSD], depressive disorder, and/or anxiety disorder) that could potentially contribute to memory deficits. Among GW veterans who met the Centers for Disease Control and Prevention criteria for chronic multisymptom illness ( $N = 272$ ), subjective memory complaint significantly predicted CVLT-II retention scores ( $\beta = -0.12$ ,  $p = 0.04$ ) and marginally predicted CVLT-II delayed recall scores ( $\beta = -0.11$ ,  $p = 0.05$ ) over and above potentially confounding demographic and clinical variables.

**CONCLUSION:** This study suggests that deployed GW veterans with subjective memory complaints have objective memory impairments. In light of the evidence linking subjective memory complaint to increased risk for dementia in the elderly, these findings suggest that aging GW veterans with subjective memory complaints should be closely monitored for further cognitive decline.

## CHRONIC FATIGUE SYNDROME

### [A Comparison of Case Definitions for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome.](#)

[Sunnquist M](#)<sup>1</sup>, [Jason LA](#)<sup>1</sup>, [Nehrke P](#)<sup>1</sup>, [Goudsmit EM](#)<sup>2</sup>.

J Chronic Dis Manag. **2017**;2(2). pii: 1013. Epub 2017 May 21.

Many professionals have described the clinical presentation of myalgic encephalomyelitis (ME), but recent efforts have focused on the development of ME criteria that can be reliably applied. The current study compared the symptoms and functioning of individuals who met the newly-developed Institute of Medicine (IOM) clinical criteria to a revised version of the London criteria for ME. While 76% of a sample diagnosed with chronic fatigue syndrome (CFS) met the IOM criteria, 44% met the revised London criteria. The revised London criteria identified patients with greater physical impairment. The results of this study indicate the need for a standard case definition with specific guidelines for operationalization. The application of case definitions has important implications for the number of individuals identified with ME, the pattern of symptoms experienced by these individuals, and the severity of their symptoms and functional limitations. Sample heterogeneity across research studies hinders researchers from replicating findings and impedes the search for biological markers and effective treatments.

**HEADACHE and MIGRAINE (Continued)****[Generalized Pain Sensitization and Endogenous Oxytocin in Individuals With Symptoms of Migraine: A Cross-Sectional Study.](#)**

[You DS](#)<sup>1</sup>, [Haney R](#)<sup>1</sup>, [Albu S](#)<sup>1,2</sup>, [Meagher MW](#)<sup>1,2</sup>.

Headache. **2017 Nov 2**. doi: 10.1111/head.13213. [Epub ahead of print]

**OBJECTIVE:** The current study examined pain and neurogenic inflammation responses to topical capsaicin during the interictal period (between headache) and their relationship with plasma oxytocin in individuals with migraine.

**BACKGROUND:** Individuals with migraine can experience generalized (extracephalic) hyperalgesia, which can persist even between headache attacks. Elevated levels of plasma and cerebrospinal fluid oxytocin have been observed during migraine attacks, oxytocin levels being positively associated with the intensity of migraine symptoms. However, whether oxytocin plays a role in the mechanisms of generalized pain sensitization and neurogenic inflammation during the interictal period has not been studied yet. Understanding migraineurs' interictal pain phenotype and endogenous oxytocin might help identify individuals who would benefit from intranasal oxytocin treatment.

**METHODS:** Thirty-two subjects with migraine and 26 healthy controls underwent pain testing. The current study compared capsaicin-induced pain, central sensitization (areas of secondary mechanical allodynia and hyperalgesia), and neurogenic inflammation (capsaicin-induced flare) responses on the nondominant volar forearm between migraineurs and healthy controls. Additionally, we studied plasma oxytocin levels and their relationship to migraine symptoms, experimental pain and affect.

**RESULTS:** The results indicated a significant group effect ( $P = .019$ ): Migraineurs reported greater capsaicin-induced pain unpleasantness ( $M = 1.2$ ,  $SD = 1.4$ ) on a 0-10 scale and showed larger areas of flare ( $\text{LnM} = 2.8$ ,  $SD = 0.4$ ) than healthy controls ( $M = 0.5$ ,  $SD = 0.8$ ;  $\text{LnM} = 2.6$ ,  $SD = 0.4$ ;  $ps < .032$ ). In a subgroup analysis, enhanced capsaicin-induced pain unpleasantness was found in the chronic ( $P = .007$ ), but not the episodic ( $Ps > .200$ ), migraineurs. The oxytocin levels were elevated in migraineurs and accounted for 18% of the group difference in capsaicin-induced pain unpleasantness. Within migraineurs, interictal oxytocin levels were negatively associated with psychological distress ( $Ps < .030$ ). However, during the interictal period, pain sensitivity in extracephalic regions and plasma oxytocin levels were unrelated to migraine symptom parameters ( $Ps > .074$ ). Lastly, the results found no group difference in areas of secondary mechanical allodynia and hyperalgesia ( $Ps > .298$ ).

**CONCLUSION:** The current study revealed that individuals with migraine exhibit enhanced extracephalic capsaicin-induced pain unpleasantness and flare responses during interictal periods. In addition, migraineurs, especially those with chronic migraine, had slightly elevated interictal oxytocin levels compared to controls, which was associated with their affective component of experimental pain. Therefore, treatment targeting affective pain during the interictal period may help to reduce generalized pain in migraine. Furthermore, endogenous increases in oxytocin may be a compensatory mechanism that may help decrease affective distress in migraineurs. The therapeutic effects of intranasal oxytocin may benefit migraineurs by reducing their affective distress.

## HEADACHE and MIGRAINE

### [Reduced motor cortical inhibition in migraine: A blinded transcranial magnetic stimulation study.](#)

[Neverdahl JP](#)<sup>1</sup>, [Omland PM](#)<sup>2</sup>, [Uglem M](#)<sup>3</sup>, [Engstrøm M](#)<sup>2</sup>, [Sand T](#)<sup>2</sup>.

Clin Neurophysiol. **2017 Sep 22**;128(12):2411-2418. doi: 10.1016/j.clinph.2017.08.032. [Epub ahead of print]

**OBJECTIVE:** To investigate motor cortical excitability, inhibition, and facilitation with navigated transcranial magnetic stimulation (TMS) in migraine in a blinded cross-sectional study.

**METHODS:** Resting motor threshold (RMT), cortical silent period (CSP), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) were compared in 27 interictal migraineurs and 33 controls. 24 female interictal migraineurs and 27 female controls were compared in subgroup analyses. Seven preictal migraineurs were also compared to the interictal group in a hypothesis-generating analysis. Investigators were blinded for diagnosis during recording and analysis of data.

**RESULTS:** SICI was decreased in interictal migraineurs when compared to healthy controls ( $p=0.013$ ), CSP was shortened in female interictal migraineurs ( $p=0.041$ ). ICF was decreased in preictal compared to interictal migraineurs ( $p=0.023$ ). RMT and ICF were not different between interictal migraineurs and controls.

**CONCLUSION:** Cortical inhibition was decreased in migraineurs between attacks, primarily in a female subgroup, indicating an importance of altered cortical inhibition in migraine.

**SIGNIFICANCE:** Previous studies on motor cortical excitability in migraineurs have yielded varying results. This relatively large and blinded study provides support for altered cortical inhibition in migraine. Measuring intracortical facilitation in the period preceding migraine attacks may be of interest for future studies.

### [New Onset Migraine Associated With a Civilian Burn Pit.](#)

[Chalela JA](#)<sup>1</sup>.

Mil Med. **2017 May**;182(5):e1812-e1813. doi: 10.7205/MILMED-D-16-00200.

**BACKGROUND:** Deployed service members exposed to burn pit smoke can experience a multitude of symptoms. Respiratory symptoms after burn pit smoke exposure are well recognized, but neurologic symptoms are less well recognized. There are reports of migraines triggered by odors but no specific reports of new onset migraines triggered by exposure to burn pit smoke. Clinicians encountering patients with new onset migraines in the deployed setting face the dilemma of evacuating the patients to perform neuroimaging or keeping them in theatre.

**METHODS:** Retrospective case series study and review of the literature.

**FINDINGS:** Three patients with new onset headache after exposure to open burn pit smoke are described. The headaches met established criteria to be classified as migraine with aura in two patients and migraine without aura in one patient. The migraines were triggered by exposure to the burn pit smoke and relieved by avoidance of the smoke. The patients did not have history of migraine and had normal neurological examinations. Computed tomography performed in one patient and optic nerve insonation performed in all three patients were normal. The patients responded well to triptans and antiemetic medicines.

**DISCUSSION:** Nociceptive odors can trigger classic migraines in adults without prior history of migraine. The temporal association between exposure to the odor and the development of the headache, the absence of abnormalities on neurologic examination, and the response to triptans help establish the diagnosis. Activation of the trigeminal system leading to release of pain-related neuropeptides may mediate the migrainous symptoms. Evacuation for advanced neuroimaging or specialized consultation can be avoided if the above-mentioned criteria are met.

## HEADACHE and MIGRAINE (Continued)

### [Human mast cells release the migraine-inducing factor pituitary adenylate cyclase-activating polypeptide \(PACAP\).](#)

[Okragly AJ](#)<sup>1</sup>, [Morin SM](#)<sup>2</sup>, [DeRosa D](#)<sup>1</sup>, [Martin AP](#)<sup>1</sup>, [Johnson KW](#)<sup>2</sup>, [Johnson MP](#)<sup>2</sup>, [Benschop RJ](#)<sup>1</sup>.

Cephalalgia. 2017 Jan 1;333102417740563. doi: 10.1177/0333102417740563. [Epub ahead of print]

**Background** Many patients with migraines suffer from allergies and vice versa, suggesting a relationship between biological mechanisms of allergy and migraine. It was proposed many years ago that mast cells may be involved in the pathophysiology of migraines. We set out to investigate the relationship between mast cell activation and known neurogenic peptides related to migraine. **Methods** Cultured human mast cells were assayed for the presence of neuropeptides and their receptors at the RNA and protein level. Immunohistochemistry analyses were performed on tissue resident and cultured mast cells. Mast cell degranulation assays were performed and pituitary adenylate cyclase-activating polypeptide (PACAP) activity was measured with a bioassay. **Results** We found that cultured and tissue resident human mast cells contain PACAP in cytoplasmic granules. No other neurogenic peptide known to be involved in migraine was detected, nor did mast cells express the receptors for PACAP or other neurogenic peptides. Furthermore, mast cell degranulation through classic IgE-mediated allergic mechanisms led to the release of PACAP. The PACAP released from mast cells was biologically active, as demonstrated using PACAP receptor reporter cell lines. We confirmed existing literature that mast cell degranulation can also be induced by several neurogenic peptides, which also resulted in PACAP release. **Conclusion** Our data provides a potential biological explanation for the association between allergy and migraine by demonstrating the release of biologically active PACAP from mast cells.

## CHRONIC PAIN

### [Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study.](#)

[Schrepf A](#)<sup>#1</sup>, [Harper DE](#)<sup>#1</sup>, [Harte SE](#)<sup>1</sup>, [Wang H](#)<sup>1</sup>, [Ichesco E](#)<sup>1</sup>, [Hampson JP](#)<sup>1</sup>, [Zubieta JK](#)<sup>2</sup>, [Clauw DJ](#)<sup>1</sup>, [Harris RE](#)<sup>1</sup>.

Pain. 2016 Oct;157(10):2217-2225. doi: 10.1097/j.pain.0000000000000633. PMID: PMC5028286.

Endogenous opioid system dysfunction potentially contributes to chronic pain in fibromyalgia (FM), but it is unknown if this dysfunction is related to established neurobiological markers of hyperalgesia. We previously reported that  $\mu$ -opioid receptor (MOR) availability was reduced in patients with FM as compared with healthy controls in several pain-processing brain regions. In the present study, we compared pain-evoked functional magnetic resonance imaging with endogenous MOR binding and clinical pain ratings in female opioid-naïve patients with FM (n = 18) using whole-brain analyses and regions of interest from our previous research. Within antinociceptive brain regions, including the dorsolateral prefrontal cortex (r = 0.81, P < 0.001) and multiple regions of the anterior cingulate cortex (all r > 0.67; all P < 0.02), reduced MOR availability was associated with decreased pain-evoked neural activity. Additionally, reduced MOR availability was associated with lower brain activation in the nucleus accumbens (r = 0.47, P = 0.050). In many of these regions, pain-evoked activity and MOR binding potential were also associated with lower clinical affective pain ratings. These findings are the first to link endogenous opioid system tone to regional pain-evoked brain activity in a clinical pain population. Our data suggest that dysregulation of the endogenous opioid system in FM could lead to less excitation in antinociceptive brain regions by incoming noxious stimulation, resulting in the hyperalgesia and allodynia commonly observed in this population. We propose a conceptual model of affective pain dysregulation in FM.

**CHRONIC PAIN (Continued)****[Chronic pain disrupts ability to work by interfering with social function: A cross-sectional study.](#)**

[Hengstebeck E](#)<sup>1</sup>, [Roskos S](#)<sup>2</sup>, [Breejen K](#)<sup>3</sup>, [Arnetz B](#)<sup>4</sup>, [Arnetz J](#)<sup>5</sup>.

Scand J Pain. 2017 Oct 26. pii: S1877-8860(17)30213-6. doi: 10.1016/j.sjpain.2017.09.021. [Epub ahead of print]

**BACKGROUND AND AIMS:** Some 100 million adults in the United States suffer from chronic pain. While research to date has focused primarily on pain interference with physical and psychological function and its effects on employment, few studies have examined the impact of pain interference on social functioning and its effects on employment. The aims of our study were to (1) evaluate the association between pain interference with ability to work and actual employment status among working age adults with chronic pain; and (2) evaluate pain interference with four types of functioning - cognitive, physical, psychological, and social - as possible mediators of pain interference with the ability to work.

**METHODS:** Data were collected via a self-selected sample of individuals visiting the American Chronic Pain Association (ACPA) website. The final dataset included 966 respondents. We examined the association between pain interference with the ability to work and employment in a population with chronic pain. We then analyzed pain interference with four types of functioning, physical, psychological, cognitive, and social, for their impact on the ability to work.

**RESULTS:** Pain interference with ability to work was significantly inversely associated with employment status, i.e., the less that pain interfered with one's ability to work, the greater the likelihood of being employed. Moreover, pain interference with ability to work was a stronger predictor of employment status than an individual's rating of their pain intensity. Pain interference with social functioning partially mediated the effects of pain interference with cognitive and physical functioning and fully mediated the effects of pain intensity and pain interference with psychological functioning on pain interference with the ability to work. Results suggest that pain interference with social function may be a significant contributor to pain interference with ability to work in working age adults with chronic pain.

**CONCLUSIONS:** In the development of effective solutions to address the economic and societal burden of chronic pain, this paper highlights the role of social function as an important, yet frequently overlooked, contributor to chronic pain's effect on the ability to work. Our findings underscore the importance of an integrated biopsychosocial approach to managing chronic pain, especially when addressing ability to work. From a clinical standpoint, assessing and managing pain intensity is necessary but not sufficient in addressing the far-reaching negative consequences of chronic pain.

**IMPLICATIONS:** The development of interventions that improve social function may improve the ability to work in adults with chronic pain. Likewise, sick leave should be prescribed restrictively in the management of chronic pain since it may further interfere with social functioning.

**PERSPECTIVE:** This study highlights the importance of the assessment of pain interference with social function as a part of a comprehensive biopsychosocial approach to the evaluation and management of patients with chronic pain. Interventions that improve social function may improve the ability to work in this population. In addition, sick leave should be prescribed restrictively in the management of chronic pain since it by itself interferes with social functioning.

## CHRONIC PAIN (Continued)

### [Cognitive Behavioral Therapy for Depression and Anxiety in an Interdisciplinary Rehabilitation Program for Chronic Pain: a Randomized Controlled Trial with a 3-Year Follow-up.](#)

[Ólason M](#)<sup>1</sup>, [Andrason RH](#)<sup>2</sup>, [Jónsdóttir IH](#)<sup>2</sup>, [Kristbergsdóttir H](#)<sup>3</sup>, [Jensen MP](#)<sup>4</sup>.

Int J Behav Med. 2017 Nov 1. doi: 10.1007/s12529-017-9690-z. [Epub ahead of print]

**PURPOSE:** Cognitive behavioral therapy (CBT) is known to be effective for treating depression and anxiety in patients with chronic pain, but there is limited research studying the long-term benefits of CBT in this population. The present study evaluated the effects of CBT provided in the context of an interdisciplinary pain management program with a 3-year follow-up.

**METHODS:** One hundred fifteen patients with chronic musculoskeletal pain participated in an interdisciplinary pain management program. Eighty of these patients meeting criteria for CBT treatment were randomized to receive or not receive CBT for depression and anxiety in addition to rehabilitation pain management. The remaining 35 patients constituted a second comparison group. Follow-up data were collected 1 and 3 years post-treatment with 19% of the patients dropping out after 1 year and 34% after 3 years. Attrition analysis did not indicate that there was significant attrition bias in the data.

**RESULTS:** All three groups evidenced improved depression following treatment ( $p < 0.001$ ). The pre- to post-treatment effect sizes (Cohen's  $d$ ) for depression in the CBT treatment group was large ( $ES = 1.36$ ). The CBT treatment group maintained improvements on all measures at a 3-year follow-up, while the comparison groups did not. This was especially evident with respect to depression (pre-treatment to 3 years follow-up  $ES = 1.35$  and between-group  $ES = 0.57$ ). Before treatment, 36% of all the patients reported that they were able to work. At 3 years post-treatment, 59%, 58%, and 44% of the patients were working who were in the CBT treatment group, the Comparison group, and the Non-CBT group, respectively.

**CONCLUSION:** The results indicate that providing CBT for depression and anxiety as part of a rehabilitation pain management program may enhance the long-term benefits of treatment. This finding, if replicated in additional studies, has important clinical and economic implications.

### [Pain Management for Primary Care Providers: A Narrative Review of High-Impact Studies, 2014-2016.](#)

[Becker WC](#)<sup>1,2</sup>, [Bair MJ](#)<sup>3</sup>, [Picchioni M](#)<sup>4</sup>, [Starrels JL](#)<sup>5</sup>, [Frank JW](#)<sup>6,7</sup>.

Pain Med. 2017 Jul 3. doi: 10.1093/pm/pnx146. [Epub ahead of print]

**Objective:** This manuscript reviews high-impact, peer-reviewed studies published from January 2014 to March 2016 that are relevant to pain management in primary care. Given the recent release of the US Centers for Disease Control and Prevention's "Guideline for Prescribing Opioids for Chronic Pain" emphasizing the primacy of nonopioid treatment, we focused our review on nonopioid pain management.

**Design:** Narrative review of peer-reviewed literature.

**Methods:** We searched three article summary services and queried expert contacts for high-impact, English-language studies related to the management of pain in adults in primary care. All authors reviewed 142 study titles to arrive at group consensus on article content domains. Within article domains, individual authors selected studies approved by the larger group according to their impact on primary care clinical practice, policy, and research, as well as quality of the study methods. Through iterative discussion, 12 articles were selected for detailed review, discussion, and presentation in this narrative review.

**Results:** We present key articles addressing each of six domains of pain management: pharmacotherapy for acute pain; interventional treatments; medical cannabis; complementary and integrative medicine; care management in chronic pain; and prevention. Within each section, we conclude with implications for pain management in primary care.

**Conclusions:** There is growing evidence for multiple nonopioid treatment modalities available to clinicians for the management of pain in primary care. The dissemination and implementation of these studies, including innovative care management interventions, warrant additional study and support from clinicians, educators, and policy-makers.

## CHRONIC PAIN (Continued)

### [Differential expression of systemic inflammatory mediators in amputees with chronic residual limb pain.](#)

[Chamessian A](#)<sup>1</sup>, [Van de Ven T](#), [Buchheit T](#), [Hsia HL](#), [McDuffie M](#), [Gamazon ER](#), [Walsh C](#), [Bruehl S](#), [Buckenmaier C](#)<sup>3rd</sup>, [Shaw A](#).

Pain. 2017 Jan;158(1):68-74. PMID: PMC5161626.

Chronic postsurgical pain impacts most amputees, with more than half experiencing neuralgic residual limb pain. The transition from normal acute postamputation pain to chronic residual limb pain likely involves both peripheral and central inflammatory mechanisms. As part of the Veterans Integrated Pain Evaluation Research study, we investigated links between systemic inflammatory mediator levels and chronic residual limb pain. Subjects included 36 recent active duty military traumatic amputees with chronic residual limb pain and 40 without clinically significant pain. Blood samples were obtained and plasma concentrations of an array of inflammatory mediators were analyzed. Residual limb pain intensity and pain catastrophizing were assessed to examine associations with inflammatory mediators. Pro-inflammatory mediators including tumor necrosis factor (TNF)- $\alpha$ , TNF- $\beta$ , interleukin (IL)-8, ICAM-1, Tie2, CRP, and SAA were elevated in patients with chronic residual limb pain. Across all patients, residual limb pain intensity was associated positively with levels of several proinflammatory mediators (IL-8, TNF- $\alpha$ , IL-12, TNF- $\beta$ , PIGF, Tie2, SAA, and ICAM-1), and inversely with concentrations of the anti-inflammatory mediator IL-13, as well as IL-2 and Eotaxin-3. Pain catastrophizing correlated positively with IL-8, IL-12, TNF- $\beta$ , PIGF, and ICAM-1, and inversely with IL-13. Significant associations between catastrophizing and residual limb pain intensity were partially mediated by TNF- $\alpha$ , TNF- $\beta$ , SAA, and ICAM-1 levels. Results suggest that chronic postamputation residual limb pain is associated with excessive inflammatory response to injury or to inadequate resolution of the postinjury inflammatory state. Impact of pain catastrophizing on residual limb pain may be because of part to common underlying inflammatory mechanisms.

## OTHER RESEARCH OF INTEREST

### [The FcRn inhibitor rozanolixizumab reduces human serum IgG concentration: A randomized phase 1 study.](#)

[Kiessling P](#)<sup>1</sup>, [Lledo-Garcia R](#)<sup>2</sup>, [Watanabe S](#)<sup>3</sup>, [Langdon G](#)<sup>4</sup>, [Tran D](#)<sup>5</sup>, [Bari M](#)<sup>5</sup>, [Christodoulou L](#)<sup>5</sup>, [Jones E](#)<sup>6</sup>, [Price G](#)<sup>5</sup>, [Smith B](#)<sup>5</sup>, [Brennan F](#)<sup>5</sup>, [White J](#)<sup>5</sup>, [Jolles S](#)<sup>7</sup>.

Sci Transl Med. 2017 Nov 1;9(414). pii: eaan1208. doi: 10.1126/scitranslmed.aan1208.

Pathogenic immunoglobulin G (IgG) autoantibodies characterize some human autoimmune diseases; their high concentration and long half-life are dependent on recycling by the neonatal Fc receptor (FcRn). Inhibition of FcRn is an attractive new treatment concept for IgG-mediated autoimmune diseases. Rozanolixizumab (UCB7665; CA170\_01519.g57 IgG4P) is an anti-human FcRn monoclonal antibody. In cynomolgus monkeys, rozanolixizumab reduced IgG (maximum 75 to 90% by about day 10), was well tolerated, and did not increase risk of infection. We also report a first-in-human, randomized, double-blind, placebo-controlled, dose-escalating study of intravenous (IV) or subcutaneous (SC) rozanolixizumab in healthy subjects (NCT02220153). The primary objective was to evaluate safety and tolerability. Secondary objectives were assessment of rozanolixizumab pharmacokinetics and pharmacodynamics, including effects on circulating IgG concentrations. Forty-nine subjects were randomized to receive rozanolixizumab (n = 36) or placebo (n = 13) across six cohorts. The first three cohorts received IV doses, and the subsequent three cohorts received SC doses, of rozanolixizumab 1, 4, or 7 mg/kg (n = 6 for each cohort; plus n = 7 or 6 for placebo, respectively). The most frequent treatment-emergent adverse event [TEAE; headache, 14 of 36 (38.9%) subjects] was dose-dependent and more prominent after IV administration. Severe TEAEs occurred in four subjects, all in the highest-dose IV group [headache (n = 3) and back pain (n = 1)]. Rozanolixizumab pharmacokinetics demonstrated nonlinear increases with dose. There were sustained dose-dependent reductions in serum IgG concentrations (IV and SC rozanolixizumab). These data provide clinical evidence for the therapeutic potential of rozanolixizumab.

**OTHER RESEARCH OF INTEREST (Continued)****[Effect of tight control management on Crohn's disease \(CALM\): a multicentre, randomised, controlled phase 3 trial.](#)**

[Colombel JF](#)<sup>1</sup>, [Panaccione R](#)<sup>2</sup>, [Bossuyt P](#)<sup>3</sup>, [Lukas M](#)<sup>4</sup>, [Baert F](#)<sup>5</sup>, [Vaňásek T](#)<sup>6</sup>, [Danalioglu A](#)<sup>7</sup>, [Novacek G](#)<sup>8</sup>, [Armuzzi A](#)<sup>9</sup>, [Hébuterne X](#)<sup>10</sup>, [Travis S](#)<sup>11</sup>, [Danese S](#)<sup>12</sup>, [Reinisch W](#)<sup>8</sup>, [Sandborn WJ](#)<sup>13</sup>, [Rutgeerts P](#)<sup>14</sup>, [Hommes D](#)<sup>15</sup>, [Schreiber S](#)<sup>16</sup>, [Neimark E](#)<sup>17</sup>, [Huang B](#)<sup>17</sup>, [Zhou Q](#)<sup>17</sup>, [Mendez P](#)<sup>18</sup>, [Petersson J](#)<sup>17</sup>, [Wallace K](#)<sup>17</sup>, [Robinson AM](#)<sup>17</sup>, [Thakkar RB](#)<sup>17</sup>, [D'Haens G](#)<sup>19</sup>.

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**BACKGROUND:** Biomarkers of intestinal inflammation, such as faecal calprotectin and C-reactive protein, have been recommended for monitoring patients with Crohn's disease, but whether their use in treatment decisions improves outcomes is unknown. We aimed to compare endoscopic and clinical outcomes in patients with moderate to severe Crohn's disease who were managed with a tight control algorithm, using clinical symptoms and biomarkers, versus patients managed with a clinical management algorithm.

**METHODS:** CALM was an open-label, randomised, controlled phase 3 study, done in 22 countries at 74 hospitals and outpatient centres, which evaluated adult patients (aged 18-75 years) with active endoscopic Crohn's disease (Crohn's Disease Endoscopic Index of Severity [CDEIS] >6; sum of CDEIS subscores of >6 in one or more segments with ulcers), a Crohn's Disease Activity Index (CDAI) of 150-450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients were randomly assigned at a 1:1 ratio to tight control or clinical management groups, stratified by smoking status (yes or no), weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years) after 8 weeks of prednisone induction therapy, or earlier if they had active disease. In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria, which differed between groups (tight control group before and after random assignment: faecal calprotectin ≥250 µg/g, C-reactive protein ≥5mg/L, CDAI ≥150, or prednisone use in the previous week; clinical management group before random assignment: CDAI decrease of <70 points compared with baseline or CDAI >200; clinical management group after random assignment: CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week). De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. The primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers 48 weeks after randomisation. Primary and safety analyses were done in the intention-to-treat population. This trial has been completed, and is registered with ClinicalTrials.gov, number [NCT01235689](#).

**FINDINGS:** Between Feb 11, 2011, and Nov 3, 2016, 244 patients (mean disease duration: clinical management group, 0.9 years [SD 1.7]; tight control group, 1.0 year [2.3]) were randomly assigned to monitoring groups (n=122 per group). 29 (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study, mostly because of adverse events. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 (56 [46%] of 122 patients) than in the clinical management group (37 [30%] of 122 patients), with a Cochran-Mantel-Haenszel test-adjusted risk difference of 16.1% (95% CI 3.9-28.3; p=0.010). 105 (86%) of 122 patients in the tight control group and 100 (82%) of 122 patients in the clinical management group reported treatment-emergent adverse events; no treatment-related deaths occurred. The most common adverse events were nausea (21 [17%] of 122 patients), nasopharyngitis (18 [15%]), and headache (18 [15%]) in the tight control group, and worsening Crohn's disease (35 [29%] of 122 patients), arthralgia (19 [16%]), and nasopharyngitis (18 [15%]) in the clinical management group.

**INTERPRETATION:** CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone. Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability.