GULF WAR ILLNESS

Pathophysiology in a model of Gulf War Illness: Contributions of pyridostigmine bromide and stress.

Macht VA[1], Woodruff JL[2], Grillo CA[2], Wood CS[2], Wilson MA[3], Reagan LP[4].

Psychoneuroendocrinology. **2018 Jul 10**;96:195-202. doi: 10.1016/j.psyneuen.2018.07.015. PMID: 30041099. [Epub ahead of print]

During the Gulf War, prophylactic treatment with pyridostigmine bromide (PB) along with the stress of deployment may have caused unexpected alterations in neural and immune function, resulting in a host of cognitive deficits which have become clinically termed Gulf War Illness (GWI). In order to test this interaction between PB and stress, the following study used a rodent model of GWI to examine how combinations of repeated restraint stress and PB induced alterations of peripheral cholinesterase (ChE) activity, corticosterone (CORT) levels, and cytokines on the last day of treatment, and then 10 days and three months post-treatment. Results indicate that PB decreases ChE activity acutely but sensitizes it by three months post-treatment selectively in rats subjected to stress. Similarly, while stress increased CORT levels acutely, rats in the PB/stressed condition continued to exhibit elevations in CORT at the delayed time point, indicating that PB and stress interact to progressively disrupt homeostasis in several peripheral measures. Because memory deficits are also common in clinical populations with GWI, we examined the effects of PB and stress on contextual fear conditioning. PB exacerbates stress-induced impairments in contextual fear conditioning ten days post-treatment, but protects against stress-induced augmentation of contextual fear conditioning at three months post-treatment. Collectively, these results provide critical insight as to how PB and stress may interact to contribute to the pathophysiological progression of GWI.

CHRONIC FATIGUE SYNDROME

Antifatigue Potential Activity of *Sarcodon imbricatus* in Acute Excise-Treated and Chronic Fatigue Syndrome in Mice via Regulation of Nrf2-Mediated Oxidative Stress.

Wang X[1], Qu Y[1], Zhang Y[1], Li S[1,2], Sun Y[1], Chen Z[1], Teng L[1,2], Wang D[1,2].

Oxid Med Cell Longev. **2018 Jun 28**;2018:9140896. doi: 10.1155/2018/9140896. PMID: 30050662. PMCID: PMC6046126. eCollection 2018.

Sarcodon imbricatus (SI), a precious edible fungus, contains 35.22% of total sugar, 18.33% of total protein, 24 types of fatty acid, 16 types of amino acid, and 8 types of minerals. Encouragingly, it is rich in potential antioxidants such as total polyphenols (0.41%), total sterols (3.16%), and vitamins (0.44%). In the present study, the antifatigue properties of SI and its potential mechanisms of action were explored by the experiments on acute excise-treated mice and chronic fatigue syndrome (CFS) mice. SI (0.25, 0.5, and 1 g/kg) significantly enhanced exercise tolerance in the weight-loaded forced swimming test (FST) and rota-rod test (RRT) and reduced the immobility in the tail suspension test on CFS mice. SI markedly increased the levels of glycogen in the liver and adenosine triphosphate (ATP) in the liver and muscle and decreased the lactic acid (LD) and blood urea nitrogen (BUN) content in both acute swimming-treated mice and CFS mice. SI improved the endogenous cellular antioxidant enzyme contents in the two mouse models by improving the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and reducing reactive oxygen species (ROS) and malondialdehyde (MDA) levels in serum, liver, and muscle, respectively. In CFS mice, the enhanced expression levels of nuclear factor erythroid-2-related factor 2 (Nrf2), SOD1, SOD2, heme oxygenase-1 (HO-1), and catalase (CAT) in the liver were observed after a 32-day SI administration. Our data indicated that SI possessed antifatigue activity, which may be related to its ability to normalize energy metabolism and Nrf2-mediated oxidative stress. Consequently, SI can be expected to serve as a novel natural antifatigue supplement in health foods.

The putative glymphatic signature of chronic fatigue syndrome: A new view on the disease pathogenesis and therapy.

Wostyn P[1], De Deyn PP[2].

Med Hypotheses. **2018 Sep**;118:142-145. doi: 10.1016/j.mehy.2018.07.007. PMID: 30037603. Epub 2018 Jul 6.

The underlying pathophysiology of chronic fatigue syndrome remains incompletely understood and there are no curative treatments for this disorder at present. However, increasing neuroimaging evidence indicates that functional and structural abnormalities exist in the brains of chronic fatigue syndrome patients, suggesting that the central nervous system is involved in this disorder and that at least some chronic fatigue syndrome patients may have an underlying neurological basis for their illness. In the present paper, we speculate that glymphatic dysfunction, causing toxic build up within the central nervous system, may be responsible for at least some cases of chronic fatigue syndrome. We further postulate that cerebrospinal fluid diversion such as lumboperitoneal shunting may be beneficial to this subgroup of patients by restoring glymphatic transport and waste removal from the brain. Although recent evidence indicates that at least some chronic fatigue syndrome patients may benefit from cerebrospinal fluid drainage, further studies are needed to confirm this finding and to determine whether this can be attributed to enhancement of glymphatic fluid flow and interstitial fluid clearance. If confirmed, this could offer promising avenues for the future treatment of chronic fatigue syndrome. Clearly, given the relative invasive nature of cerebrospinal fluid diversion, such procedures should be reserved for chronic fatigue syndrome patients who are severely debilitated, or for those with severe headaches. Anyhow, it seems worthwhile to make every effort to identify new therapies for patients who suffer from this devastating disease, especially given that there are currently no effective treatments for this condition.

HEADACHE and MIGRAINE

Cluster headache beyond the pain phase: A prospective study of 500 attacks.

Snoer A[1], Lund N[2], Beske R[2], Hagedorn A[2], Jensen RH[2], Barloese M[2].

Neurology. **2018 Jul 27**. pii: 10.1212/01.wnl.0000542491.92981.03. doi: 10.1212/01.wnl.0000542491.92981.03. PMID: 30054443.

OBJECTIVE: To describe the nature, prevalence, and duration of symptoms in the preictal, ictal, and postictal phases of cluster headache (CH) attacks.

METHODS: Fifty-seven patients with episodic or chronic CH participated in this prospective, observational study. In a questionnaire concerning 33 CH and migraine-related symptoms, patients reported the clinical features of up to 10 CH attacks/patient. The questionnaire was divided into 3 sections: a preictal phase, ictal phase, and postictal phase. For each phase, patients documented whether the given symptom was present, and if possible estimated the duration of the symptom.

RESULTS: In total, 500 CH attack descriptions were obtained. In the preictal phase, general symptoms (most frequently concentration difficulties, restlessness, and mood changes) occurred 20 minutes prior to 46.0% of attacks. Local painful and autonomic symptoms were observed 10 minutes prior to 54.6% and 35% of attacks, respectively. Postictally, pain and autonomic symptoms resolved over 20 minutes, leaving patients with fatigue (36.2%), decreased energy (39.0%), and concentration difficulties (27.6%), lasting a median of 60 minutes.

CONCLUSIONS: Preictal and postictal symptoms are very frequent in CH, demonstrating that CH attacks are not composed of a pain phase alone. Since the origin of CH attacks is unresolved, studies of preictal and postictal symptoms could contribute to the understanding of CH pathophysiology and, potentially, early, abortive treatment strategies.

Poor sleep quality in migraine and probable migraine: a population study.

Song TJ[1], Cho SJ[2], Kim WJ[3], Yang KI[4], Yun CH[5], Chu MK[6].

J Headache Pain. **2018 Jul 25**;19(1):58. doi: 10.1186/s10194-018-0887-6. PMID: 30046921.

BACKGROUND: Probable migraine (PM) is a subtype of migraine that is prevalent in the general population. Previous studies have shown that poor sleep quality is common among migraineurs and is associated with an exacerbation of migraine symptoms. However, information on the prevalence and clinical implication of poor sleep quality among individuals with PM is scarce. Thus, the aim of this study was to assess the prevalence and clinical impact of poor sleep quality in individuals with PM in comparison with those with migraine.

METHODS: Two-stage cluster random sampling was used to perform the survey for sleep and headache in Korean general population. Participants with Pittsburgh Sleep Quality Index > 5 were considered as having poor sleep quality.

RESULTS: Of 2695 participants, 379 (14.1%) had PM and 715 (26.5%) had poor sleep quality. Prevalence of poor sleep quality was 35.4% in the PM group, which was lower than that in the migraine group (47.6%, $p = 0.011$), but higher than that in the non-headache group (21.4%, $p < 0.001$). The PM participants with poor sleep quality showed increased headache frequency (median [interquartile range]: 2.0 [0.3-4.0] vs. 1.0 [0.2-2.0]; $p = 0.001$) and headache intensity (visual analogue scale, 6.0 [4.0-7.0] vs. 5.0 [3.5-6.0]; $p = 0.003$) compared to PM participants who had no poor sleep quality.

CONCLUSIONS: Poor sleep quality was prevalent among participants with PM. It was associated with an exacerbation of PM symptoms. Our findings suggest that proper evaluation and treatment for poor sleep quality are needed in the management of PM.

HEADACHE and MIGRAINE (Continued)

Migraine in adults with diabetes; is there an association? Results of a population-based study.

López-de-Andrés A[1], Luis Del Barrio J[1], Hernández-Barrera V[1], de Miguel-Díez J[2], Jimenez-Trujillo I[1], Martinez-Huedo MA[3], Jimenez-García R[1].

Diabetes Metab Syndr Obes. **2018 Jul 20**;11:367-374. doi: 10.2147/DMSO.S170253. PMID: 30050314. PMCID: PMC6056164. eCollection 2018.

Aims: To investigate the association between migraine and diabetes mellitus while controlling for several socio-demographic characteristics, comorbidities, and lifestyle variables. We also aimed to identify which of these variables are associated with migraine among diabetics.

Patients and methods: We conducted a cross-sectional study using data taken from the European Health Interview Surveys for Spain conducted in 2009/10 (n=22,188) and 2014 (n=22,842). We selected those subjects ≥40 years of age. Diabetes status was self-reported. One non-diabetic control was matched by the year of survey, age, and sex for each diabetic case. The presence of migraine was defined as the affirmative answer to both of the following questions: "Have you suffered migraine or frequent headaches over the last 12 months?" and "Has your physician confirmed the diagnosis?". Independent variables included demographic and socio-economic characteristics, health status variables, lifestyle, and pain characteristics.

Results: The prevalence of migraine was significantly higher among those suffering from diabetes (14.9% vs. 13.0%; *p*=0.021). The multivariable analysis showed that diabetes was not associated with a higher risk of migraine (adjusted OR 1.06; 95%CI 0.89-1.25). Among diabetic subjects, female sex, suffering concomitant mental disorders, respiratory disorders, neck pain, and low back pain were variables associated with suffering from migraine.

Conclusion: We found no significant differences in the prevalence of migraine between diabetics and non-diabetic age- and sex-matched controls after controlling for possible confounders.

Headache in transient ischemic attacks.

Lebedeva ER[1,2], Gurary NM[3], Olesen J[4].

J Headache Pain. **2018 Jul 27**;19(1):60. doi: 10.1186/s10194-018-0888-5. PMID: 30054753.

BACKGROUND: Headache is a common feature in acute cerebrovascular disease but no studies have evaluated the prevalence of specific headache types in patients with transient ischemic attacks (TIA). The purpose of the present study was to analyze all headaches within the last year and the last week before TIA and at the time of TIA.

METHODS: Eligible patients with TIA (n = 120, mean age 56.1, females 55%) had focal brain or retinal ischemia with resolution of symptoms within 24 h without presence of new infarction on MRI with DWI (n = 112) or CT (n = 8). All patients were evaluated within one day of admission by a single neurologist. As a control group we used patients (n = 192, mean age 58.7, females 64%) admitted with diagnoses "lumbago", "lumbar spine osteochondrosis" or "gastrointestinal ulcer".

RESULTS: One-year prevalence of migraine without aura was significantly higher in TIA patients than in controls: 20.8% and 7.8% respectively (p = 0.002, OR 3.1, 95% CI 1.6-6.2). 22 patients (18.3%) had sentinel or warning headache within the last week before TIA. At the time of TIA a new type of headache was observed in 16 patients (13.3%). No controls had a new type of headache. 12 of these 16 patients had migraine-like headache, 8 patients had tension-type-like headache and one patient thunderclap headache. Posterior circulation TIA was associated with headaches within last week before TIA and at the time of TIA much more frequently than anterior circulation TIA.

CONCLUSIONS: The one year prevalence of migraine was significantly higher in TIA patients than in controls and so was the prevalence of headache within the last week before TIA and at the time of TIA. A previous headache that worsens and a new type of headache can be a warning of impending TIA.

HEADACHE and MIGRAINE (Continued)

The Effect of Regional Anesthetic Sphenopalatine Ganglion Block on Self-Reported Pain in Patients With Status Migrainosus.

Mehta D[1], Leary MC[1,2], Yacoub HA[1,2], El-Hunjul M[1], Kincaid H[1], Koss V[1,2], Wachter K[2], Malizia D[3], Glassman B[4], Castaldo JE[5].

Headache. **2018 Jul 25**. doi: 10.1111/head.13390. PMID: 30043973. [Epub ahead of print]

BACKGROUND: Status migrainosus (SM) is defined as a debilitating migraine attack lasting more than 72 hours in patients previously known to suffer from migraine headache. Typically, these attacks fail to respond to over the counter and abortive medications. The sphenopalatine ganglion (SPG) plays a critical role in propagating both pain and the autonomic symptoms commonly associated with migraines. SPG block via transnasal lidocaine is moderately effective in reducing migraine symptoms, but this approach is often poorly tolerated and the results are inconsistent. We proposed that an SPG block using a suprazygomatic injection approach would be a safe and effective option to abort or alleviate pain and autonomic symptoms of SM.

METHODS: Through a retrospective records review, we identified patients with a well-established diagnosis of migraine, based on the International Headache Society criteria. Patients selected for study inclusion were diagnosed with SM, had failed to respond to 2 or more abortive medications, and had received a suprazygomatic SPG block. Patients had also been asked to rate their pain on a 1-10 Likert scale, both before and 30 minutes after the injection.

RESULTS: Eighty-eight consecutive patients (20 men and 68 women) received a total of 252 suprazygomatic SPG block procedures in the outpatient headache clinic after traditional medications failed to abort their SM. At 30 minutes following the injections, there was a 67.2% (±26.6%) reduction in pain severity with a median reduction of 5 points (IQR= -6 to -3) on the Likert scale (ranging from 1 to 10). Overall, patients experienced a statistically significant reduction in pain severity ($P < .0001$).

CONCLUSION: The SPG is known to play an integral role in the pathophysiology of facial pain and the trigeminal autonomic cephalalgias, although its exact role in the generation and maintenance of migraine headache remains unclear. Regional anesthetic suprazygomatic SPG block is potentially effective for immediate relief of SM. We believe the procedure is simple to perform and has minimal risk.

Combination of Ayurveda and Yoga therapy reduces pain intensity and improves quality of life in patients with migraine headache.

Sharma VM[1], Manjunath NK[2], Nagendra HR[2], Ertsey C[3].

Complement Ther Clin Pract. **2018 Aug**;32:85-91. doi: 10.1016/j.ctcp.2018.05.010. PMID: 30057065. Epub 2018 May 31.

OBJECTIVES: To Understand the efficacy of Ayurveda and Yoga in the management of Migraine Headache.

METHODS: 30 subjects recruited to Ayurveda and Yoga (AY) group underwent traditional Panchakarma (Bio-purificatory process) using therapeutic Purgation followed by Yoga therapy, while 30 subjects of Control (CT) group continued on symptomatic treatment (NSAID's) for 90 days. Body constitution questionnaire was administered to both groups. The outcome measures included Symptom check list, Comprehensive Headache related Quality of Life Questionnaire and Visual Analogue Scale.

RESULTS: Forty-six (76.6%) out of 60 subjects belonging to both groups had Pitta based body constitution. Following 90 days of intervention the AY group showed significant reduction in Migraine symptoms including pain intensity ($p < .001$) and improvement in Headache related Quality of Life ($p < .001$). The CT group showed no significant change ($p > .05$).

CONCLUSION: Traditional Ayurveda along with Yoga therapy reduces symptoms, intensity of pain and improves Quality of life in Migraine patients.

CHRONIC PAIN

Functional brain connectivity and cortical thickness in relation to chronic pain in post-911 veterans and service members with mTBI.

Newsome MR[1], Wilde EA[1,2], Bigler ED[3], Liu Q[1], Mayer AR[4], Taylor BA[5], Steinberg JL[6], Tate DF[7], Abildskov TJ[3], Scheibel RS[1], Walker WC[8], Levin HS[1].

Brain Inj. **2018 Jul 26**:1-9. doi: 10.1080/02699052.2018.1494853. PMID: 30047797. [Epub ahead of print]

OBJECTIVES: Investigate the relation of chronic pain interference to functional connectivity (FC) of brain regions and to cortical thickness in post-911 Veterans and Service Members (SMs) who sustained a mild traumatic brain injury (mTBI).

METHODS: This is an observational study with cross-sectional analyses. A sample of 65 enrollees completing initial evaluation at a single site of the Chronic Effects of Neurotrauma Consortium (CENC) reported pain interference ratings on the TBI QOL. Functional connectivity and cortical thickness were measured.

RESULTS: Severity of pain interference was negatively related to FC of the default mode network (DMN), i.e., participants who reported more severe pain interference had less FC between mesial prefrontal cortex and posterior regions of the DMN including posterior cingulate cortex and precuneus. Cortical thickness of specific regions was positively related to severity of pain interference.

CONCLUSION: The more that pain was perceived to interfere with daily life, the less the FC between regions in a network associated with self-referential thought and mind wandering. Although cortical thickness in specific brain regions was positively related to severity of pain interference, follow-up longitudinal data, control group data, and study of individual differences in this cohort will expand this initial report and replicate these findings.

Interleukin-27 controls basal pain threshold in physiological and pathological conditions.

Sasaguri T[1], Taguchi T[2,3], Murata Y[4], Kobayashi K[5], Iizasa S[6], Iizasa E[7], Tsuda M[8], Hirakawa N[1], Hara H[7], Yoshida H[9], Yasaka T[10].

Sci Rep. **2018 Jul 23**;8(1):11022. doi: 10.1038/s41598-018-29398-3. PMID: 30038376.

Numerous studies have shown that pain sensation is affected by various immune molecules, such as cytokines, in tissues comprising the sensory pathway. Specifically, it has been shown that interleukin (IL)-17 promotes pain behaviour, but IL-10 suppresses it. IL-27 has been reported to have an anti-inflammatory effect through regulation of T cell differentiation, resulting in reduced IL-17 and induction of IL-10. Thus, we hypothesised that IL-27 would have some regulatory role in pain sensation. Here, we provide evidence that endogenous IL-27 constitutively controls thresholds for thermal and mechanical sensation in physiological and pathological conditions. Mice lacking IL-27 or its receptor WSX-1 spontaneously showed chronic pain-like hypersensitivity. Reconstitution of IL-27 in IL-27-deficient mice reversed thermal and mechanical hypersensitive behaviours. Thus, unlike many other cytokines induced by inflammatory events, IL-27 appears to be constitutively produced and to control pain sensation. Furthermore, mice lacking IL-27/WSX-1 signalling showed additional hypersensitivity when subjected to inflammatory or neuropathic pain models. Our results suggest that the mechanisms underlying hypersensitive behaviours caused by the ablation of IL-27/WSX-1 signalling are different from those underlying established chronic pain models. This novel pain control mechanism mediated by IL-27 might indicate a new mechanism for the chronic pain hypersensitivity.

CHRONIC PAIN (Continued)

Shared genetic influence on frailty and chronic widespread pain: a study from TwinsUK.

Livshits G[1,2], Ni Lochlainn M[3], Malkin I[2], Bowyer R[1], Verdi S[1], Steves CJ[1,3], Williams FMK[1].

Age Ageing. **2018 Jan 1**;47(1):119-125. doi: 10.1093/ageing/afx122. PMID: 28985290. PMCID: PMC5860041.

Introduction: frailty is an increased vulnerability to adverse health outcomes, across multiple physiological systems, with both environmental and genetic drivers. The two most commonly used measures are Rockwood's frailty index (FI) and Fried's frailty phenotype (FP).

Material and methods: the present study included 3626 individuals from the TwinsUK Adult Twin Registry. We used the classical twin model to determine whether FI and FP share the same latent aetiological factors. We also investigated the relationship between frailty and chronic widespread musculoskeletal pain (CWP), another holistic age-related condition with significant clinical impact.

Results: FP and FI shared underlying genetic and environmental aetiology. CWP was associated with both frailty measures, and health deficits appeared to mediate the relationship between phenotypic frailty and pain. Latent genetic factors underpinning CWP were shared with frailty. While frailty was increased in the twins reporting pain, co-twin regression analysis indicated that the relationship between CWP and frailty is reduced after accounting for shared genetic and environmental factors.

Conclusions: both measures of frailty tap the same root causes, thus this work helps unify frailty research. We confirmed a strong association between CWP and frailty, and showed a large and significant shared genetic aetiology of both phenomena. Our findings argue against pain being a significant causative factor in the development of frailty, favouring common causation. This study highlights the need to manage CWP in frail individuals and undertake a Comprehensive Geriatric Assessment in individuals presenting with CWP. Finally, the search for genetic factors underpinning CWP and frailty could be aided by integrating measures of pain and frailty.

New Therapy for Refractory Chronic Mechanical Low Back Pain-Restorative Neurostimulation to Activate the Lumbar Multifidus: One Year Results of a Prospective Multicenter Clinical Trial.

Deckers K[1], De Smedt K[1], Mitchell B[2], Vivian D[2], Russo M[3], Georgius P[4], Green M[5], Vieceli J[5], Eldabe S[6], Gulve A[6], van Buyten JP[7], Smet I[7], Mehta V[8], Ramaswamy S[8], Baranidharan G[9], Sullivan R[10], Gassin R[10], Rathmell J[11], Gilligan C[11].

Neuromodulation. **2018 Jan**;21(1):48-55. doi: 10.1111/ner.12741. PMID: 29244235. PMCID: PMC5814827. Epub 2017 Dec 15.

OBJECTIVES: The purpose of the international multicenter prospective single arm clinical trial was to evaluate restorative neurostimulation eliciting episodic contraction of the lumbar multifidus for treatment of chronic mechanical low back pain (CMLBP) in patients who have failed conventional therapy and are not candidates for surgery or spinal cord stimulation (SCS).

MATERIALS AND METHODS: Fifty-three subjects were implanted with a neurostimulator (ReActiv8, Mainstay Medical Limited, Dublin, Ireland). Leads were positioned bilaterally with electrodes close to the medial branch of the L2 dorsal ramus nerve. The primary outcome measure was low back pain evaluated on a 10-Point Numerical Rating Scale (NRS). Responders were defined as subjects with an improvement of at least the Minimal Clinically Important Difference (MCID) of ≥2-point in low back pain NRS without a clinically meaningful increase in LBP medications at 90 days. Secondary outcome measures included Oswestry Disability Index (ODI) and Quality of Life (QoL; EQ-5D).

RESULTS: For 53 subjects with an average duration of CLBP of 14 years and average NRS of 7 and for whom no other therapies had provided satisfactory pain relief, the responder rate was 58%. The percentage of subjects at 90 days, six months, and one year with ≥MCID improvement in single day NRS was 63%, 61%, and 57%, respectively. Percentage of subjects with ≥MCID improvement in ODI was 52%, 57%, and 60% while those with ≥MCID improvement in EQ-5D was 88%, 82%, and 81%. There were no unanticipated adverse events (AEs) or serious AEs related to the device, procedure, or therapy. The initial surgical approach led to a risk of lead fracture, which was mitigated by a modification to the surgical approach.

CONCLUSIONS: Electrical stimulation to elicit episodic lumbar multifidus contraction is a new treatment option for CMLBP. Results demonstrate clinically important, statistically significant, and lasting improvement in pain, disability, and QoL.

OTHER RESEARCH OF INTEREST

Pretreatment Rostral Anterior Cingulate Cortex Theta Activity in Relation to Symptom Improvement in Depression: A Randomized Clinical Trial.

Pizzagalli DA[1], Webb CA[1], Dillon DG[1], Tenke CE[2], Kayser J[2], Goer F[1], Fava M[3], McGrath P[2], Weissman M[2], Parsey R[4], Adams P[2], Trombello J[5], Cooper C[5], Deldin P[6], Oquendo MA[7], McInnis MG[6], Carmody T[5], Bruder G[2], Trivedi MH[5].

JAMA Psychiatry. **2018 Jun 1**;75(6):547-554. doi: 10.1001/jamapsychiatry.2018.0252.

Importance: Major depressive disorder (MDD) remains challenging to treat. Although several clinical and demographic variables have been found to predict poor antidepressant response, these markers have not been robustly replicated to warrant implementation in clinical care. Increased pretreatment rostral anterior cingulate cortex (rACC) theta activity has been linked to better antidepressant outcomes. However, no prior study has evaluated whether this marker has incremental predictive validity over clinical and demographic measures.

Objective: To determine whether increased pretreatment rACC theta activity would predict symptom improvement regardless of randomization arm.

Design, Setting, and Participants: A multicenter randomized clinical trial enrolled outpatients without psychosis and with chronic or recurrent MDD between July 29, 2011, and December 15, 2015 (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care [EMBARC]). Patients were consecutively recruited from 4 university hospitals: 634 patients were screened, 296 were randomized to receive sertraline hydrochloride or placebo, 266 had electroencephalographic (EEG) recordings, and 248 had usable EEG data. Resting EEG data were recorded at baseline and 1 week after trial onset, and rACC theta activity was extracted using source localization. Intent-to-treat analysis was conducted. Data analysis was performed from October 7, 2016, to January 19, 2018.

Interventions: An 8-week course of sertraline or placebo.

Main Outcomes and Measures: The 17-item Hamilton Rating Scale for Depression score (assessed at baseline and weeks 1, 2, 3, 4, 6, and 8).

Results: The 248 participants (160 [64.5%] women, 88 [35.5%] men) with usable EEG data had a mean (SD) age of 36.75 (13.15) years. Higher rACC theta activity at both baseline (b = -1.05; 95% CI, -1.77 to -0.34; P = .004) and week 1 (b = -0.83; 95% CI, -1.60 to -0.06; P < .04) predicted greater depressive symptom improvement, even when controlling for clinical and demographic variables previously linked with treatment outcome. These effects were not moderated by treatment arm. The rACC theta marker, in combination with clinical and demographic variables, accounted for an estimated 39.6% of the variance in symptom change (with 8.5% of the variance uniquely attributable to the rACC theta marker).

Conclusions and Relevance: Increased pretreatment rACC theta activity represents a nonspecific prognostic marker of treatment outcome. This is the first study to date to demonstrate that rACC theta activity has incremental predictive validity.

Trial Registration: clinicaltrials.gov Identifier: NCT01407094.

Suicidal ideation in non-depressed individuals: The effects of a chronic, misunderstood illness.

Devendorf AR[1], McManimen SL[1], Jason LA[1].

J Health Psychol. **2018 Jul 1**:1359105318785450. doi: 10.1177/1359105318785450. PMID: 29992837. [Epub ahead of print]

Chronic illness is a risk factor for suicide but is often explained with depression. Research has shown an increased suicide rate in patients with myalgic encephalomyelitis and chronic fatigue syndrome, but specific risk factors have been unexplored. We qualitatively analyzed responses from 29 patients who endorsed suicidal ideation but did not meet depression criteria. Two themes were developed: (1) feeling trapped and (2) loss of self, loss of others, stigma and conflict. Myalgic encephalomyelitis and chronic fatigue syndrome caused patients severe disability, restructured their lives, and inflicted serious pain. Participants emphasized that they were not depressed, but felt trapped by the lack of treatments available.

OTHER RESEARCH OF INTEREST (Continued)

Incidence of Endemic Human Cutaneous Leishmaniasis in the United States.

McIlwee BE[1,2], Weis SE[2], Hosler GA[1,2,3].

JAMA Dermatol. **2018 Jul 25**. doi: 10.1001/jamadermatol.2018.2133. PMID: 30046836. [Epub ahead of print]

Importance: Leishmaniasis is recognized as an endemic human disease in Africa, the Middle East, Asia, and South America. Yet despite case reports of endemic human leishmaniasis in the United States, and well-documented occurrences of disease in various animal vectors and reservoirs, the endemicity of leishmaniasis in North America has not yet been established. Moreover, leishmaniasis is not a federally reportable disease in the United States. Clinical awareness of endemic disease therefore remains low, with North American physicians considering leishmaniasis a tropical disease.

Objective: To assess the endemicity of human leishmaniasis in the United States.

Design, Setting, and Participants: This cross-sectional multicenter observational study reviewed cases of human leishmaniasis occurring in the United States from 2007 through 2017. Previously diagnosed, deidentified cases of leishmaniasis were reported by the institutions of the authors and acknowledged contributors, as well as the Texas Department of State Health Services. Cases of leishmaniasis were identified by searching by disease name (leishmaniasis) or International Classification of Diseases, 9th and 10th Revisions diagnosis codes in the respective laboratory information systems.

Exposures: Via examination of deidentified demographics, cases of leishmaniasis were classified as one of the following: (1) documentation of no history of travel outside of the United States within 10 years; (2) positive history of travel outside of the United States within 10 years; or (3) unknown or no documentation of travel history.

Main Outcomes and Measures: Cases of leishmaniasis were considered endemic if identified in patients with documentation of no travel history outside of the United States within 10 years.

Results: Of the 69 novel cases of human cutaneous leishmaniasis identified in this study, 41 (59%) were endemic; the median age at diagnosis was 61 years (range, 3-89 years), and 28 (68%) of the endemic cases occurred in female patients. Twenty-two (32%) cases had documentation of Leishmania speciation performed by polymerase chain reaction, and in 100% of these cases the infectious organism was identified as Leishmania mexicana.

Conclusions and Relevance: Human cutaneous leishmaniasis is endemic in the United States, and, at least regionally, is acquired endemically more frequently than it is via travel. Our data argue in favor of making leishmaniasis a federally reportable disease and may have substantial implications on North American public health initiatives, with climate models predicting the number of citizens exposed to leishmaniasis will double by 2080.

Assessment of outcomes following high-dose opioid tapering in a Veterans Healthcare System.

Hundley L[1], Spradley S[2], Donelenko S[2].

J Opioid Manag. **2018 Mar/Apr**;14(2):89-101. doi: 10.5055/jom.2018.0436. PMID: 29733095.

OBJECTIVE: To assess the impact of tapering of chronic high dose opioid therapy in veterans prompted by the implementation of the Opioid Safety Initiative in 2013.

DESIGN: IRB and VA Office of Research and Development-approved retrospective, observational chart review.

SETTING: North Florida/South Georgia Veterans Health System Patients: Veterans on high dose opioid therapy (≥300 mg of morphine equivalents per day) for chronic non-cancer pain as of 1/1/2012 with an opioid agreement discontinuation note documented in the medical record were included. Veterans treated for cancer pain or under palliative care were excluded.

OUTCOMES: Descriptive outcomes include rate of opioid discontinuation, average duration of tapering, and rate of relapse. Differences before and after discontinuation assessed include healthcare utilization, monitoring via urine drug screens and state prescription drug monitoring program (PDMP) queries, non-opioid analgesics, benzodiazepines, and non-pharmacologic modalities.

RESULTS: Forty-three patients were included. The mean duration of therapy was 7.8 years and 81.4 percent were on methadone prior to tapering. Opioids were tapered to discontinuation in 28 patients (65 percent) with long-term abstinence in 71 percent. The mean duration of tapering was 81 days and the median/mode was 30 days. Statistically significant differences after tapering include decreased PDMP queries, increased non-opioid analgesics, decreased benzodiazepine prescriptions, and increased use of mental health services ($p < 0.05$). There were zero adverse outcomes identified in those tapered and one death in the group who sought non-VA care for continuation.

CONCLUSIONS: This study suggests that moderate speed tapering in high-risk veterans on chronic high-dose opioid therapy can be achieved, but caution is warranted in ensuring adequate follow-up and monitoring. Clinical pharmacy services may improve tapering outcomes by providing more frequent follow-up, monitoring via state PDMP queries to identify patients who have relapsed, and dispensing naloxone for increased safety.

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