GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial.

Clark LV[1], Pesola F[2], Thomas JM[3], Vergara-Williamson M[4], Beynon M[5], White PD[5].

Link to full text of Article in *The Lancet*.

Comment in:
Comment Abstract below on page 2. Link to full text of Comment in *The Lancet*.

BACKGROUND: Graded exercise therapy is an effective and safe treatment for chronic fatigue syndrome, but it is therapist intensive and availability is limited. We aimed to test the efficacy and safety of graded exercise delivered as guided self-help.

METHODS: In this pragmatic randomised controlled trial, we recruited adult patients (18 years and older) who met the UK National Institute for Health and Care Excellence criteria for chronic fatigue syndrome from two secondary-care clinics in the UK. Patients were randomly assigned to receive specialist medical care (SMC) alone (control group) or SMC with additional guided graded exercise self-help (GES). Block randomisation (randomly varying block sizes) was done at the level of the individual with a computer-generated sequence and was stratified by centre, depression score, and severity of physical disability. Patients and physiotherapists were necessarily unmasked from intervention assignment; the statistician was masked from intervention assignment. SMC was delivered by specialist doctors but was not standardised; GES consisted of a self-help booklet describing a six-step graded exercise programme that would take roughly 12 weeks to complete, and up to four guidance sessions with a physiotherapist over 8 weeks (maximum 90 min in total). Primary outcomes were fatigue (measured by the Chalder Fatigue Questionnaire) and physical function (assessed by the Short Form-36 physical function subscale); both were self-rated by patients at 12 weeks after randomisation and analysed in all randomised patients with outcome data at follow-up (ie, by modified intention to treat). We recorded adverse events, including serious adverse reactions to trial interventions. We used multiple linear regression analysis to compare SMC with GES, adjusting for baseline and stratification factors. This trial is registered at ISRCTN, number ISRCTN22975026.

FINDINGS: Between May 15, 2012, and Dec 24, 2014, we recruited 211 eligible patients, of whom 107 were assigned to the GES group and 104 to the control group. At 12 weeks, compared with the control group, mean fatigue score was 19·1 (SD 7·6) in the GES group and 22·9 (6·9) in the control group (adjusted difference -4·2 points, 95% CI -6·1 to -2·3, p<0·0001; effect size 0·53) and mean physical function score was 55·7 (23·3) in the GES group and 50·8 (25·3) in the control group (adjusted difference 6·3 points, 1·8 to 10·8, p=0·006; 0·20). No serious adverse reactions were recorded and other safety measures did not differ between the groups, after allowing for missing data.

INTERPRETATION: GES is a safe intervention that might reduce fatigue and, to a lesser extent, physical disability for patients with chronic fatigue syndrome. These findings need confirmation and extension to other health-care settings.

FUNDING: UK National Institute for Health Research Research for Patient Benefit Programme and the Sue Estermann Fund.

CHRONIC FATIGUE SYNDROME (Continued)

Guided graded exercise self-help as a treatment of fatigue in chronic fatigue syndrome.

Clauw DJ[1].

Comment on: Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. [Lancet. 2017]

Link to full text of Comment Article in *The Lancet*.

In *The Lancet*, Lucy Clark and colleagues show that, in the GETSET trial (n=211), patients with chronic fatigue syndrome who were treated with a 12 week guided graded exercise self-help programme in addition to ongoing specialist medical care had significantly lower mean fatigue score (reduction by 4·2 points [95% CI 2·3–6·1], p<0·0001; effect size 0·53) and higher self-reported physical function score (increase by 6·3 points [1·8–10·8], p=0·006; effect size 0·20) than did patients managed with specialist medical care alone. This pragmatic randomised controlled trial was done at two secondary-care centres in the UK, and its findings support the results of the previously reported PACE trial[2]—ie, that graded exercise therapy is an effective treatment for chronic fatigue syndrome—although the GETSET trial involved much less intensive use of physiotherapists. In the GETSET trial, physiotherapists guided the patients through graded exercise using a self-help booklet, and face-to-face contact was minimal (maximum of one episode of face-to-face contact, and then up to three other appointments via telephone or Skype not lasting more than 90 min in total). The finding that graded exercise therapy is effective even when exercise is not being witnessed and directly guided by a physiotherapist is a substantial advance, since many patients with chronic fatigue syndrome and other functional impairment have difficulty getting to physiotherapy or do not have access to appropriately trained physiotherapists. (Continues in *Lancet*.)

A reboot for chronic fatigue syndrome research.

Maxmen A.

Link to briefing review article in Nature summarizing past and present treatment, research, and controversies about Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS). Excerpt follows:

After decades of pleading, people with the condition [chronic fatigue syndrome (ME/CFS)] have finally caught the attention of mainstream science — and dozens of exploratory studies are now under way. Scientists entering the field are using the powerful tools of modern molecular biology to search for any genes, proteins, cells and possible infectious agents involved. They hope the work will yield a laboratory test to diagnose ME/CFS — which might have several different causes and manifestations — and they want to identify molecular pathways to target with drugs.

The US National Institutes of Health (NIH) in Bethesda, Maryland, bolstered the field last year by more than doubling spending for research into the condition, from around US$6 million in 2016 to $15 million in 2017. Included in that amount are funds for four ME/CFS research hubs in the United States that will between them receive $36 million over the next five years.

The stakes are high because the field's scientific reputation has been marred by controversial research. A 2009 report that a retrovirus called XMRV could underlie the disease was greeted with fanfare only to be retracted two years later. And in 2011 and 2013, a British team reported that exercise and cognitive behavioural therapy relieved the symptoms of ME/CFS for many people in a large clinical study called the PACE trial. US and UK health authorities had made recommendations based on the findings, but, starting around 2015, scientists and patient advocates began publicly criticizing the trial for what they saw as flaws in its design. The organizers of the trial deny that there were serious problems with it, but health officials in both countries have nevertheless been revising their guidelines.

Patients, meanwhile, are adrift in a vacuum of knowledge about the condition, says Jose Montoya, an infectious-disease specialist at Stanford Medical School in California and one of Allen's physicians. "ME/CFS has suffered from scientists applying the usual approaches," he says. He hopes that sophisticated analyses of genomics, proteomics, metabolomics and more will help to change that. "It wasn't until the microscope became available that an Italian microbiologist could link cholera to the bacteria that caused it," he says. "In the same sense, we have not had the equivalent to the microscope until now."

CHRONIC FATIGUE SYNDROME (Continued)

Elevations of Ventricular Lactate Levels Occur in Both Chronic Fatigue Syndrome and Fibromyalgia.

Natelson BH[1], Vu D[1], Coplan JD[2], Mao X[3], Blate M[1], Kang G[3], Soto E[4], Kapusuz T[4], Shungu DC[3].

Background: Chronic fatigue syndrome (CFS) and fibromyalgia (FM) frequently have overlapping symptoms, leading to the suggestion that the same disease processes may underpin the two disorders - the unitary hypothesis. However, studies investigating the two disorders have reported substantial clinical and/or biological differences between them, suggesting distinct pathophysiological underpinnings.

Purpose: The purpose of this study was to further add to the body of evidence favoring different disease processes in CFS and FM by comparing ventricular cerebrospinal fluid lactate levels among patients with CFS alone, FM alone, overlapping CFS and FM symptoms, and healthy control subjects.

Methods: Ventricular lactate was assessed in vivo with proton magnetic resonance spectroscopic imaging (^{1}H MRSI) with the results normed across the 2 studies in which the data were collected.

Results: Mean CSF lactate levels in CFS, FM and CFS+FM did not differ among the three groups, but were all significantly higher than the mean values for control subjects.

Conclusion: While patients with CFS, FM and comorbid CFS and FM can be differentiated from healthy subjects based on measures of CFS lactate, this neuroimaging outcome measure is not a viable biomarker for differentiating CFS from FM or from patients in whom symptoms of the two disorders overlap.

HEADACHE and MIGRAINE

Gamma-aminobutyric acid (GABA) receptors GABRA4, GABRE, and GABRQ gene polymorphisms and risk for migraine.

García-Martín E[1,2,3], Esguevillas G[1], Serrador M[4], Alonso-Navarro H[5,6], Navacerrada F[5,7], Amo G[1], García-Albea E[6], Agúndez JAG[1,2,3], Jiménez-Jiménez FJ[8,9].

Several biochemical, pharmacological, neurophysiological and experimental data suggest a possible role of gamma-aminobutyric acid (GABA) in the pathogenesis of migraine. We investigated the possible association of the most common single nucleotide polymorphisms (SNPs) in the GABA receptor alpha4 (GABRA4), epsilon (GABRE), and theta (GABRQ) genes with the risk for migraine. A TaqMan-based qPCR assay designed to detect the most common SNPs in the GABRA4 (rs2229940), GABRE (rs1139916), and GABRQ (rs3810651) was performed in 197 migraine patients and 394 age- and gender-matched controls. The possible influence of gender, age at onset of migraine, positive family history of migraine, presence or absence of aura, and triggering of migraine by ethanol on the frequency of the genotypes was also studied. The frequency of GABRE rs1139916AA genotype was significantly lower in the migraine group only in the female gender, but the differences did not reach statistical significance after correction for multiple comparisons. The mean ± SD age at onset of migraine was significantly lower in patients with GABRQ rs3810651AA as compared with the other two genotypes. Positive family history of migraine and presence or absence of aura did not influence the frequencies of the genotypes of the three SNPs studied. Triggering of migraine by ethanol was significantly less frequent in patients with GABRA4 rs2229940GG and more frequent in patients with GABRQ 3810651TT genotype, but the differences lost statistical significance after correction for multiple comparisons. GABRQ rs3810651 could play a role in the modification of age at onset of migraine.

HEADACHE and MIGRAINE (Continued)

Chronic migraine, comorbidity, and socioeconomic deprivation: cross-sectional analysis of a large nationally representative primary care database.

McLean G[1], Mercer SW[1].

Background: Chronic migraine is common but there is limited knowledge on associated comorbidities.

Objectives: To examine mental and physical comorbidities in chronic migraine and the influence of socioeconomic status in a large, nationally representative dataset.

Design: Analysis of cross-sectional primary healthcare data from 1,468,404 adults in Scotland. Chronic migraine, 31 other physical conditions, and seven mental health conditions we examined. Prevalence rates were standardized by age groups, sex, and socioeconomic deprivation, and adjusted odds ratio (aOR) and 95% confidence intervals (CI) calculated for those with chronic migraine compared with those without.

Results: Chronic migraine patients had more conditions, with the biggest difference found for five or more conditions (chronic migraine 11.7% vs. controls 4.9%; aOR 3.00; 95% CI 2.78-3.22). Twenty-five of the 31 physical conditions were significantly more prevalent in the chronic migraine group. The biggest difference was for chronic pain (aOR 4.33; 95% CI 4.12-4.55). For mental health conditions, the biggest differences were for anxiety (aOR 2.95; 95% CI 2.76-31.5) and depression (aOR 2.94; 95% CI 2.81-3.08). Increasing deprivation was associated with more severe and complex comorbidity (five or more conditions), and with more combined mental and physical comorbidity in the chronic migraine group.

Conclusions: In a large nationally representative sample in primary care, comorbidity was most common in those with chronic migraine compared with standardized controls, and this was exacerbated by living in areas of higher deprivation.

Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers.

Dahri M[1], Tarighat-Esfanjani A[2], Asghari-Jafarabadi M[3], Hashemilar M[4].

BACKGROUNDS AND AIMS: Migraine and inflammation are correlated. Coenzyme Q10 (CoQ10) as an anti-inflammatory agent has shown useful effects in other diseases. The present study aimed to assess the effect of CoQ10 supplementation on inflammation and clinical features of migraine.

METHODS: This randomized double-blind placebo-controlled clinical trial was conducted among 45 non-menopausal women aged 18-50 years, diagnosed for episodic migraine according to the International Headache Society. After one month run-in period, subjects received CoQ10 (400 mg/day CoQ10, n = 23) or placebo (wheat starch, n = 22) for three months. All the patients got prophylactic medication too. Serum CoQ10 concentration, Calcitonin gene-related peptide (CGRP), interleukin (IL)-6, IL-10 and tumor necrosis factor-α (TNF-α) were measured at the beginning and end of the study.

RESULTS: CoQ10 supplementation reduced CGRP and TNF-α significantly (p = 0.011 and p = 0.044, respectively), but there were no significant differences in serum IL-6 and IL-10 between the two groups. Significant increase in serum CoQ10 levels was evident with CoQ10 therapy (P < 0.001). A significant improvement was found in frequency (p = 0.018), severity (p = 0.001) and duration (p = 0.012) of migraine attacks in CoQ10 group compared to placebo.

CONCLUSION: CoQ10 supplementation may decrease CGRP and TNF-α with no favorable effects on IL-6 and IL-10 in patients with migraine.

HEADACHE and MIGRAINE (Continued)

Headache in the first manifestation of Multiple Sclerosis - Prospective, multicenter study.

Gebhardt M[1], Kropp P[2], Jürgens TP[3], Hoffmann F[1], Zettl UK[4].

Objectives: Multiple sclerosis (MS) is the most frequent immune-mediated inflammation of the central nervous system that can lead to early disability. Headaches have not been considered as MS-related symptoms initially, whereas higher prevalence rates were reported since 2000. Postmortem histological analyses of MS patients' brains revealed lymphoid follicle-like structures in the cerebral meninges which suggest a possible pathophysiological explanation for the high headache prevalence in MS. The aim of this study was to evaluate headache characteristics during the first clinical event of MS.

Methods: In a prospective, multicenter study, 50 patients with the diagnosis of CIS or MS were recruited. All participants were screened for the presence of headache within the last 4 weeks with help of the Rostock Headache Questionnaire (Rokoko).

Results: Thirty-nine of fifty questioned patients (78%) reported headaches within the last 4 weeks. Most patients suffered from throbbing and pulsating headaches (25, 50%), 15 (30%) reported stabbing, 14 (28%) dull and constrictive headaches.

Conclusions: Headaches were prevalent in 78% of patients in our population with newly diagnosed CIS and MS. It is among the highest prevalence rates reported so far in patients with CIS or MS. Thus, headache, especially of a migraneous subtype, is a frequent symptom within the scope of the first manifestation of multiple sclerosis. If it were possible to define a MS-typical headache, patients with these headaches and with typical MRI results would be classified as CIS or early MS instead of radiologically isolated syndrome and treated accordingly with an immunomodulatory therapy.

CHRONIC PAIN

Number and Type of Post-Traumatic Stress Disorder (PTSD) Symptom Domains are Associated with Patient-Reported Outcomes in Patients with Chronic Pain.

Langford DJ, Theodore BR, Balsiger D, Tran C, Doorenbos AZ, Tauben DJ, Sullivan MD.

Post-Traumatic Stress Disorder (PTSD) commonly accompanies complex chronic pain, yet PTSD is often overlooked in chronic pain management. Using the 4-item Primary Care (PC)-PTSD screening tool, we evaluated the relationship between the number and type of PC-PTSD symptoms endorsed and a set of patient-reported outcomes, including: pain intensity and interference; function; mood; quality of life; and substance abuse risk in a consecutive sample of patients with chronic pain (n=4,402). Patients completed PainTracker™, a web-based patient-reported outcome tool that provides a multidimensional evaluation of chronic pain, as part of their intake evaluation at a specialty pain clinic in a community setting. Twenty-seven percent of the sample met PC-PTSD screening criteria for PTSD by endorsing three of the four symptom domains. Significant ordinal trends were observed between increasing number of PTSD symptoms and all outcomes evaluated. The occurrence of even one PTSD symptom was associated with overall poorer outcomes, suggesting that subsyndromal PTSD is clinically significant in the context of chronic pain. Among the four PTSD domains assessed, "numbness/detachment" was most strongly associated with negative pain outcomes by relative weight analysis. Results from this cross-sectional study suggest that a range of pain-related outcomes may be significantly related to co-morbid PTSD.

PERSPECTIVE: We present evidence that PTSD symptoms are significantly related to a broad set of pain-related patient-reported outcomes. These findings highlight the need to evaluate for PTSD symptoms in patients with chronic pain, especially feelings of numbness or detachment from others, in order to improve understanding and management of chronic pain.

CHRONIC PAIN (Continued)

Are Group Size and Composition Associated with Treatment Outcomes in Group Cognitive Behavioural Therapy for Chronic Pain?

Wilson D[1], Sc MA, Mackintosh S[1], Nicholas MK[2], Moseley GL[1,3], Costa D[2], Ashton-James C[2].

This study explored whether group size and group member characteristics (age, gender, compensation status) were associated with patient outcomes (changes in pain and disability). Retrospective analyses of outcome data obtained from two independently run group Cognitive Behavioural Therapy (CBT) programs for chronic pain (Program A: N = 317 and Program B: N = 693) were conducted. Intracluster correlations (ICCs) were significant in both studies, indicating group-level effects on patient outcomes in both group CBT programs for chronic pain. Mixed modelling revealed that group size and group member characteristics (age, gender, and compensation status) were related to patient outcomes, but not consistently across programs. The results of our analyses confirm the contribution of group composition to individual treatment outcomes in group CBT for chronic pain, and highlight factors that have the potential to contribute to group-level variability in patient outcomes. Further research is needed to identify the mechanisms that account for the impact of group characteristics on the efficacy of CBT for chronic pain.

Pain self-management training increases self-efficacy, self-management behaviours and pain and depression outcomes.

Damush TM[1,2,3,4,5], Kroenke K[1,4,5], Bair MJ[1,4,5], Wu J[6], Tu W[5,6], Krebs EE[7,8], Poleshuck E[9].

BACKGROUND: Self-management practices among patients with medical and psychiatric comorbidity is not well understood. We assessed the effects of a combined pharmacological and behavioural intervention on self-efficacy to manage symptoms and self-management behaviours in patients with pain and comorbid depression.

METHODS: Longitudinal analysis of self-management behaviours and their relationship with outcomes in a 12-month trial of 250 primary care patients with chronic musculoskeletal pain and comorbid depression. Participants were randomized to either usual care or an intervention that consisted of optimized antidepressant therapy followed by six sessions of a pain self-management (PSM) programme.

RESULTS: Participants in the intervention group significantly increased the time spent performing self-management behaviours including strengthening and stretching exercises, progressive muscle relaxation and visualization at 12 months. Moreover, intervention participants reported greater self-efficacy to manage their pain and depression. The number of pain self-management sessions received showed a dose-response relationship with improvement in both pain and depression severity.

CONCLUSION: A combined intervention increased patient self-management behaviours and self-efficacy to manage symptoms among primary care patients with chronic musculoskeletal pain and depression. Receipt of the full dose of the entire PSM programme was related to improvements in pain interference and depression severity. WHAT DOES THIS STUDY ADD?: A nurse-led six-session PSM programme increased self-efficacy as well as specific behaviours such as strengthening and stretching exercises, progressive muscle relaxation and visualization. There was a dose-response in that attending a greater proportion of the PSM sessions led to greater improvement in both pain and depression outcomes.

CHRONIC PAIN (Continued)

Fibromyalgia has a high prevalence and impact in cardiac failure patients.

Gist AC[1], Guymer EK[1], Ajani AE[1,2], Littlejohn GO[1].

Objective: Chronic cardiac failure (CCF) shares several clinical features with fibromyalgia (FM), a syndrome of increased central sensitivity and musculoskeletal pain. FM frequently coexists with other chronic illness. Musculoskeletal pain is reported in patients with CCF; however, the prevalence and impact of FM in patients with CCF is not known. This research aims to assess the prevalence and effects of concurrent FM in patients with CCF and to identify other coexisting central sensitivity syndromes.

Material and Methods: In a cross-sectional study, demographic, clinical, and functional information was gathered from participants with CCF from public and private clinics. Cardiac failure severity was rated using the New York Heart Association (NYHA) scale. FM diagnosis was determined using 2011 American College of Rheumatology (ACR) criteria. The short-form 36 (SF-36) assessed overall health function.

Results: Of the 57 CCF participants (63.2% male, mean age 70.3 years), 22.8% (n=13) met FM diagnostic criteria. CCF patients with FM had poorer outcomes across multiple SF-36 domains (p<0.05), compared to those without, despite having comparable CCF severity. Those with FM were more likely to report other central sensitivity syndromes, especially temporomandibular joint dysfunction (mean Δ=23%, p<0.05), headache (mean Δ=28.8%, p<0.05), and irritable bladder (mean Δ=14%, p<0.05).

Conclusion: High prevalence of FM was found in patients with CCF. This was associated with increased likelihood of other comorbid central sensitivity syndromes and with poorer clinical outcomes. The recognition of coexisting FM in patients with CCF provides an important opportunity to improve health outcomes by managing FM-related symptoms, in addition to symptoms that relate specifically to CCF.

OTHER RESEARCH OF INTEREST

Precision editing of the gut microbiota ameliorates colitis.

Zhu W[1], Winter MG[1], Byndloss MX[2], Spiga L[1], Duerkop BA[3], Hughes ER[1], Büttner L[1], de Lima Romão E[2], Behrendt CL[3], Lopez CA[2], Sifuentes-Dominguez L[4], Huff-Hardy K[5], Wilson RP[6], Gillis CC[1], Tükel Ç[6], Koh AY[1,4], Burstein E[5], Hooper LV[3,7], Bäumler AJ[2], Winter SE[1].

Link to full text in Nature.

Inflammatory diseases of the gastrointestinal tract are frequently associated with dysbiosis, characterized by changes in gut microbial communities that include an expansion of facultative anaerobic bacteria of the Enterobacteriaceae family (phylum Proteobacteria). Here we show that a dysbiotic expansion of Enterobacteriaceae during gut inflammation could be prevented by tungstate treatment, which selectively inhibited molybdenum-cofactor-dependent microbial respiratory pathways that are operational only during episodes of inflammation. By contrast, we found that tungstate treatment caused minimal changes in the microbiota composition under homeostatic conditions. Notably, tungstate-mediated microbiota editing reduced the severity of intestinal inflammation in mouse models of colitis. We conclude that precision editing of the microbiota composition by tungstate treatment ameliorates the adverse effects of dysbiosis in the inflamed gut.

OTHER RESEARCH OF INTEREST (Continued)

[What Makes for Successful Registry Implementation: A Qualitative Comparative Analysis.](#)

[Holtrop JS](#)[1], [Hall TL](#)[2], [Rubinson C](#)[2], [Dickinson LM](#)[2], [Glasgow RE](#)[2].

PURPOSE: Registry implementation is an important component of successfully achieving patient-centered medical home designation and an important part of population-based health. The purpose of this study was to examine what factors are evident in the successful implementation of a registry in a selection of Colorado practices involved in quality-improvement activities.

METHODS: In-depth, small-group interviews occurred at 13 practices. The data were recorded, transcribed, and qualitatively analyzed to identify key themes regarding elements of successful registry implementation. Key elements were described as conditions, then calibrated and analyzed using qualitative comparative analysis (QCA).

RESULTS: The QCA revealed several formulas to successful registry implementation. Key conditions included the importance of Resources and Leadership along with either a Quality Improvement Mindset or a Key Person driving efforts (or both). Health System membership affected the specific formula.

DISCUSSION: This study is innovative in that it examines which factors and in what combination are necessary for successful implementation of a registry. The findings have implications for primary care quality-improvement efforts.

[β-Arrestin-biased β-adrenergic signaling promotes extinction learning of cocaine reward memory.](#)

[Huang B](#)[1], [Li Y](#)[1], [Cheng D](#)[1], [He G](#)[1], [Liu X](#)[2], [Ma L](#)[2].

Link to full text in [Science Signaling](#).

Extinction learning of cocaine-associated contextual cues can help prevent cocaine addicts from relapsing. Pharmacological manipulation of β-adrenergic receptor (β-AR) during extinction learning is being developed as a potential strategy to treat drug addiction. We demonstrated that the extinction learning of cocaine-associated memory was mediated by β-arrestin2-biased but not heterotrimeric guanine nucleotide-binding protein (G protein)-dependent β-adrenergic signaling. We found that administration of the nonbiased β-AR antagonist propranolol, but not the G protein-biased β-AR antagonist carvedilol, blocked extinction learning of cocaine-conditioned place preference and the associated ERK activation in the infralimbic prefrontal cortex. Overexpression of β-arrestin2 in the infralimbic prefrontal cortex promoted extinction learning, which was blocked by propranolol. Knockout of β-arrestin2 in the infralimbic prefrontal cortex, specifically in excitatory neurons, impaired extinction learning of cocaine-conditioned place preference, which was not rescued by carvedilol. β-Arrestin2 signaling in infralimbic excitatory neurons was also required for the extinction learning in the cocaine self-administration model. Our results suggest that β-arrestin-biased β-adrenergic signaling in the infralimbic prefrontal cortex regulates extinction learning of cocaine-associated memories and could be therapeutically targeted to treat addiction.

[The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome.](#)

[Silber MH](#)[1], [Becker PM](#)[2], [Buchfuhrer MJ](#)[3], [Earley CJ](#)[4], [Ondo WG](#)[5], [Walters AS](#)[6], [Winkelman JW](#)[7]; [Scientific and Medical Advisory Board, Restless Legs Syndrome Foundation](#).

Restless legs syndrome (RLS) is a distinct disorder, differing from chronic pain in many ways. Refractory RLS is characterized by unresponsiveness to dopamine agonists or alpha-2-delta ligands due to inadequate efficacy, augmentation, or adverse effects. This may result in severely impaired quality of life, profound insomnia, and suicidal depression. Opioid therapy is a mainstay in the management of these patients. This article summarizes the basic science and clinical evidence in support of their use, including the positive result of a large controlled multicenter study of 306 subjects, and outlines an approach to their use in clinical practice. Treatable explanations for RLS refractoriness, such as low iron stores, and other therapeutic options, such as combination therapy, should be considered before prescribing opioids. The agents most commonly used are oxycodone and methadone, but tramadol, codeine, morphine, and hydrocodone can also be considered. Controlled-release medication should be used for evening dosage and short-acting drugs, if needed, during the day. Effective doses are considerably lower than used for chronic pain (oxycodone 10-30 mg daily; methadone 5-20 mg daily) and the risk of opioid use disorder is relatively low. However, sensible precautions should be undertaken, including assessing opioid risk with standard questionnaires, using an opioid contract, using urine drug screens, consulting state prescription drug monitoring programs, and frequent reevaluation of effectiveness and side effects. Opioid use in selected patients with refractory RLS may be life-transforming with favorable risk-benefit ratio.

OTHER RESEARCH OF INTEREST (Continued)

Effects of IL1B single nucleotide polymorphisms on depressive and anxiety symptoms are determined by severity and type of life stress.

Kovacs D[1], Eszlari N[2], Petschner P[2], Pap D [3], Vas S[2], Kovacs P[4], Gonda X[5], Juhasz G[6], Bagdy G[2].

Interleukin-1β is one of the main mediators in the cross-talk between the immune system and the central nervous system. Higher interleukin-1β levels are found in mood spectrum disorders, and the stress-induced expression rate of the interleukin-1β gene (IL1B) is altered by polymorphisms in the region. Therefore we examined the effects of rs16944 and rs1143643 single nucleotide polymorphisms (SNPs) within the IL1B gene on depressive and anxiety symptoms, as measured by the Brief Symptom Inventory, in a Hungarian population sample of 1053 persons. Distal and proximal environmental stress factors were also included in our analysis, namely childhood adversity and recent negative life-events. We found that rs16944 minor (A) allele specifically interacted with childhood adversity increasing depressive and anxiety symptoms, while rs1143643's minor (A) allele showed protective effect against depressive symptoms after recent life stress. The genetic main effects of the two SNPs were not significant in the main analysis, but the interaction effects remained significant after correction for multiple testing. In addition, the effect of rs16944 A allele was reversed in a subsample with low-exposure to life stress, suggesting a protective effect against depressive symptoms, in the post hoc analysis. In summary, both of the two IL1B SNPs showed specific environmental stressor-dependent effects on mood disorder symptoms. We also demonstrated that the presence of exposure to childhood adversity changed the direction of the rs16944 effect on depression phenotype. Therefore our results suggest that it is advisable to include environmental factors in genetic association studies when examining the effect of the IL1B gene.

Cardiovascular Guideline Skepticism vs Lifestyle Realism?

Greenland P[1,2].

Link to full text of Viewpoint Article in JAMA.

The recent release of a new practice guideline for the prevention, detection, evaluation, and management of high blood pressure in adults—a report from the American College of Cardiology and the American Heart Association—has received substantial attention by the medical community and from the news media. The news overload is reminiscent of similar media attention that accompanied new cholesterol guidelines and a new risk calculator when those reports were issued by the same organizations in 2013. In addition to the "news" about the guidelines, there have been almost predictable concerns raised as well. How could the "experts" have gotten it so wrong? How could a panel, constituted by these 2 highly respected organizations and with one of the most rigorous approaches to development of practice guidelines, have been so misguided?

Both the lipid guideline and the new blood pressure guideline are lengthy documents, so long and dense, in fact, that many who have raised concerns may not have actually read them. Perhaps more worrisome is that some are leveling criticism at the guidelines for making too many individuals in the United States "sick" or labeling them with a disease. After the cholesterol guideline appeared, some critics decried the fact that the "new guideline" turned billions of people into candidates for statins. Now, very quickly, some critics are claiming that too many people will be defined as hypertensive because of a new lower threshold for diagnosis and treatment of hypertension.

Reviewing the details of the guidelines are beyond the scope of this Viewpoint. The guidelines are comprehensive and well supported by high-quality evidence. Every one of the recommendations in each guideline was given a grade of evidence, and many of the recommendations that are considered contentious by some who have raised concern are based on high-quality clinical trial evidence. So, is the problem with the guidelines, with the interpretation of the evidence, or with the notion that, somehow, the guidelines are responsible for defining too many people as having a condition that may require treatment?

It is time to turn attention away from the guidelines as part of the problem and, instead, focus on the real problem: too many individuals in the United States have cardiovascular risk factors that are unhealthy and place them at risk for a host of diseases including coronary heart disease (CHD), stroke, peripheral vascular disease, dementia, diabetes, cancer, and others. The US way of life is the problem, not the guidelines, and those who have raised concerns would do more good if they were to focus on the facts related to the US lifestyle instead of depicting the problem as being caused by the guidelines. Individuals must take more responsibility for their own health behaviors. (Continues in full-text of JAMA article.)

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