GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

**Chronic Fatigue Syndrome: From Chronic Fatigue to More Specific Syndromes.**
Blitshteyn S1, Chopra P2.

In the last decade, a group of chronic disorders associated with fatigue (CDAF) emerged as the leading cause of chronic fatigue, chronic pain, and functional impairment, all of which have been often labeled in clinical practice as chronic fatigue syndrome (CFS) or fibromyalgia. While these chronic disorders arise from various pathophysiologic mechanisms, a shared autoimmune or immune-mediated etiology could shift the focus from symptomatic treatment of fatigue and pain to targeted immunomodulatory and biological therapy. A clinical paradigm shift is necessary to reevaluate CFS and fibromyalgia diagnoses and its relationship to the CDAF entities, which would ultimately lead to a change in diagnostic and therapeutic algorithm for patients with chronic fatigue and chronic pain. Rather than uniformly apply the diagnoses of CFS or fibromyalgia to any patient presenting with unexplained chronic fatigue or chronic pain, it may be more beneficial and therapeutically effective to stratify these patients into more specific diagnoses in the CDAF group.

**Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).**
Rasa S1, Nora-Krukle Z1, Henning N2, Eliassen E2, Shikova E3, Harrer T4, Scheibenbogen C5, Murovska M1, Prusty BK6,7; European Network on ME/CFS (EUROMENE).

BACKGROUND AND MAIN TEXT: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and controversial clinical condition without having established causative factors. Increasing numbers of cases during past decade have created awareness among patients as well as healthcare professionals. Chronic viral infection as a cause of ME/CFS has long been debated. However, lack of large studies involving well-designed patient groups and validated experimental set ups have hindered our knowledge about this disease. Moreover, recent developments regarding molecular mechanism of pathogenesis of various infectious agents cast doubts over validity of several of the past studies.

CONCLUSIONS: This review aims to compile all the studies done so far to investigate various viral agents that could be associated with ME/CFS. Furthermore, we suggest strategies to better design future studies on the role of viral infections in ME/CFS.
HEADACHE and MIGRAINE

**Burden of Migraine in Europe Using Self-Reported Digital Diary Data from the Migraine Buddy© Application.**
Vo P1, Paris N2, Bilitou A3, Valena T4, Fang J5, Naujoks C6, Cameron A7, de Reydet de Vulpillieres F6, Cadiou F2.

**INTRODUCTION:** Migraine is a neurological disease characterized by recurring attacks that can cause severe disabling pain. This study described the burden of migraine as reported by individuals with migraine in the real world using a mobile application.

**METHODS:** A retrospective, cross-sectional analysis was conducted using data captured through the Migraine Buddy© smartphone application from adult, self-diagnosed individuals with migraine in 17 European countries. Data were analyzed descriptively for the most recent 28-day period reported by users (n = 3900) during the study period (June 2015-July 2016) who were randomly selected on the basis of data completeness (completion rates > 70%) and stratified by migraine headache days/month: 4-7 episodic migraine (EM; n = 1500), 8-14 EM (n = 1500), and chronic migraine (≥ 15; CM; n = 900).

**RESULTS:** More than 95% of users reported that migraine negatively affected their daily activities during at least one migraine attack. Attacks affected 50.5% (184.4 days/year), 26.9% (98 days/year), and 14.5% (53 days/year) of the year among CM, 8-14 EM, and 4-7 EM groups, respectively. On average, 44.8% CM, 40.9% 8-14 EM, and 34.7% of 4-7 EM sufferers, respectively, reported anxiety and/or depression symptoms during migraine attacks. Social or home activities, productivity, and sleep were highly affected, regardless of migraine frequency. Employed respondents (n = 3106) reported an average of 2.3 workdays missed per month and that at least one in four migraines led to work absenteeism; these migraines were commonly reported to have at least moderate to severe levels of pain, corresponding to the inability of persons to perform some or even any activities. Triptans (68%), opioids (46%), and nonsteroidal anti-inflammatory drugs (45%) were self-reported as the most common medicines used.

**CONCLUSIONS:** This study, leveraging patient-reported data collected through a mobile application, demonstrates the high burden and impact of migraine on health-related quality of life, work productivity, and overall well-being of individuals suffering from migraines.

**FUNDING:** Novartis Pharma AG, Switzerland.

**Insufficient Sleep in Tension-Type Headache: A Population Study.**
Oh JH1, Cho SJ2, Kim WJ3, Yang KI4, Yun CH5, Chu MK6.

**BACKGROUND AND PURPOSE:** Sufficient sleep is an essential part of good health and well-being. Tension-type headache (TTH) is the most common type of primary headache and has negative impacts on the quality of life and work performance. We aimed to determine the relationship between TTH and insufficient sleep in the general population.

**METHODS:** This study used data from the Korean Headache Sleep Study, which was a population-based survey about headache and sleep among Korean adults. Insufficient sleep was defined when the discrepancy between sleep need and average sleep duration was at least 1 hour.

**RESULTS:** Among the 2,695 included subjects, 570 (21.2%) and 727 (27.0%) were classified as having TTH and insufficient sleep, respectively. The prevalence of insufficient sleep was significantly higher among subjects with TTH than among those without headaches (28.8% vs. 20.4%). For subjects with TTH, the scores on a visual analogue scale (4.7±1.8 vs. 4.3±1.9, mean±SD) and the Headache Impact Test-6 (44.9±7.0 vs. 43.6±6.1) were much higher in subjects with insufficient sleep than in those without insufficient sleep. Multivariable analyses revealed that insomnia [odds ratio (OR)=2.1], poor sleep quality (OR=1.7), and short sleep duration (OR=6.9) were significantly associated with insufficient sleep in subjects with TTH.

**CONCLUSIONS:** Our findings suggest that insufficient sleep is prevalent among subjects with TTH and is linked to an exacerbation of TTH. Therefore, the proper evaluation and management of sleep may lead to the better management of TTH.
HEADACHE and MIGRAINE (Continued)

**Early onset of efficacy with erenumab in patients with episodic and chronic migraine.**
Schwedt T1, Reuter U2, Tepper S3, Ashina M4, Kudrow D5, Broessner G6, Boudreau GP7, McAllister P8, Vu T9, Zhang F9, Cheng S9, Picard H9, Wen S10, Kahn J10, Klatt J11, Mikol D9.

**BACKGROUND:** Subcutaneous erenumab reduced monthly migraine days and increased the likelihood of achieving a ≥ 50% reduction at all monthly assessment points tested in 2 pivotal trials in episodic migraine (EM) and chronic migraine (CM). Early efficacy of migraine preventive medications is an important treatment characteristic to patients. Delays in achievement of efficacy can result in failed adherence. The objective of these post-hoc analyses were to evaluate efficacy in the first 4 weeks after initial subcutaneous administration of erenumab 70 mg, erenumab 140 mg, or placebo.

**METHODS:** There is no generally accepted methodology to measure onset of action for migraine preventive medications. We used a comprehensive approach with data from both studies to evaluate change from baseline in weekly migraine days (WMD), achievement of ≥ 50% reduction in WMD, and proportion of patients experiencing migraine measured on a daily basis. The 7-day moving averages were overlaid with observed data.

**RESULTS:** In both studies (EM: N = 955; CM: N = 667), there was evidence of onset of efficacy of erenumab vs. placebo during the first week of treatment, which in some cases reached nominal significance. For EM the changes in WMD were (least squares mean [LSM] [95% CI]): placebo, -0.1 (-0.3, 0.0); erenumab 70 mg, -0.3 (-0.5, -0.2) p = 0.130; erenumab 140 mg, -0.6 (-0.7, -0.4) p < 0.001. For CM the changes were: placebo, -0.5 (-0.8, -0.3); erenumab 70 mg, -0.9 (-1.2, -0.7) p = 0.047; erenumab 140 mg, -0.8 (-1.1, -0.5) p = 0.18. Achievement of ≥ 50% reduction in WMD was observed as early as Week 1 (adjusted OR [95% CI] erenumab vs placebo) in EM: erenumab 70 mg, 1.3 (1.0, 1.9) p = 0.097; erenumab 140 mg, 2.0 (1.4, 2.7) p < 0.001. A similar outcome was observed for CM: erenumab 70 mg, 1.8 (1.1, 2.8) p = 0.011; erenumab 140 mg, 1.9 (1.2, 2.9) p = 0.009. Seven-day moving averages of observed data showed each treatment arm differed from placebo by Week 1 (OR [95% CI]): in EM Day 3 for erenumab 140 mg, 0.7 (0.5, 1.0) p = 0.031 and at Day 7 for 70 mg, 0.6 (0.4, 0.8) p = 0.002; in CM: Day 6 for erenumab 70 mg, 0.6 (0.4, 0.9) p = 0.022 and at Day 7 for 140 mg, 0.7 (0.4, 1.0); p = 0.038.

**CONCLUSION:** Erenumab showed early onset of efficacy with separation from placebo within the first week of treatment in both chronic and episodic migraine patients.

**Increased use of illicit drugs in a Dutch cluster headache population.**
de Coo IF1,2, Naber WC1, Wilbrink LA1, Haan J1,3, Ferrari MD1, Fronczek R1,4.

**Introduction:** Many patients with cluster headache report use of illicit drugs. We systematically assessed the use of illicit drugs and their effects in a well-defined Dutch cluster headache population.

**Methods:** In this cross-sectional explorative study, 756 people with cluster headache received a questionnaire on lifetime use and perceived effects of illicit drugs. Results were compared with age and sex-matched official data from the Dutch general population.

**Results:** Compared to the data from the general population, there were more illicit drug users in the cluster headache group (31.7% vs. 23.8%; p < 0.01). Reduction in attack frequency was reported by 56% (n = 22) of psilocybin mushroom, 60% (n = 3) of lysergic acid diethylamide and 50% (n = 2) of heroin users, and a decreased attack duration was reported by 46% (n = 18) of PSI, 50% (n = 2) of heroin and 36% (n = 8) of amphetamine users.

**Conclusion:** In the Netherlands, people with cluster headache use illicit drugs more often than the general population. The question remains whether this is due to an actual alleviatory effect, placebo response, conviction, or common pathophysiological background between cluster headache and addictive behaviours such as drug use.
CHRONIC PAIN

**Relationship Between Chronic Conditions and Disability in African American Men and Women.**

**BACKGROUND:** Race differences in chronic conditions and disability are well established; however, little is known about the association between specific chronic conditions and disability in African Americans. This is important because African Americans have higher rates and earlier onset of both chronic conditions and disability than white Americans.

**METHODS:** We examined the relationship between chronic conditions and disability in 602 African Americans aged 50 years and older in the Baltimore Study of Black Aging. Disability was measured using self-report of difficulty in activities of daily living (ADL). Medical conditions included diagnosed self-reports of asthma, depressive symptoms, arthritis, cancer, diabetes, cardiovascular disease (CVD), stroke, and hypertension.

**RESULTS:** After adjusting for age, high school graduation, income, and marital status, African Americans who reported arthritis (women: odds ratio (OR)=4.87; 95% confidence interval (CI): 2.92-8.12; men: OR=2.93; 95% CI: 1.36-6.30) had higher odds of disability compared to those who did not report having arthritis. Women who reported major depressive symptoms (OR=2.59; 95% CI: 1.43-4.69) or diabetes (OR=1.83; 95% CI: 1.14-2.95) had higher odds of disability than women who did not report having these conditions. Men who reported having CVD (OR=2.77; 95% CI: 1.03-7.41) had higher odds of disability than men who did not report having CVD.

**CONCLUSIONS:** These findings demonstrate the importance of chronic conditions in understanding disability in African Americans and how it varies by gender. Also, these findings underscore the importance of developing health promoting strategies focused on chronic disease prevention and management to delay or postpone disability in African Americans.

**PUBLICATION INDICES:** Pubmed, Pubmed Central, Web of Science database.

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**Profiles of Subjective Well-being in Patients with Chronic Back Pain: Contrasting Subjective and Objective Correlates.**
Wettstein M, Eich W, Bieber C, Tesarz J.

**Objective:** The detrimental impact of nonspecific chronic low back pain (CLBP) on quality of life is well known. However, patients with CLBP represent a remarkably heterogeneous group, and not all of them report compromised well-being.

**Methods:** In this study, we investigated this heterogeneity by identifying profiles (or clusters) of well-being and their correlates in 239 CLBP patients. To take the multidimensionality of subjective well-being into account, we included multiple well-being indicators (depression, anxiety, affective distress, perceived control over life). For an in-depth characterization of the well-being profiles, we assessed 1) sociodemographic indicators (age, gender, education, marital status, occupational status), 2) pain-related measures (pain intensity, subjective and objective pain disability, number of pain locations), 3) psychosocial resources (mental health, resilience, perceived support), 4) biographical factors (trauma), and 5) somatosensory profiles based on quantitative sensory testing.

**Results:** Based on two-step cluster analysis, we identified three distinct well-being profiles, characterized by either generally high well-being (cluster 1, n = 51), moderate well-being (cluster 2, n = 104), or consistently low well-being (cluster 3, n = 77), respectively. Most differences between the derived well-being profiles regarding sociodemographic, psychosocial, and biographical measures were of weak to moderate effect size. Larger effect sizes were observed for differences in pain intensity and subjective, but not objective, pain disability. Finally, the largest effects were found for differences in psychosocial resources.

**Conclusions:** Our findings suggest that not only in nonclinical samples, but also in patients with chronic pain, well-being is more closely associated with psychological resources and subjective evaluations than with objective parameters.
CHRONIC PAIN (Continued)

**Pain intensity as a moderator of the association between opioid use and insomnia symptoms among adults with chronic pain.**

Miller MB¹, Chan WS², Curtis AF¹, Boissonaute J ³, Robinson M³, Staud R⁴, Berry RB⁴, McCrae CS⁵.


OBJECTIVE: Research documenting the impact of opioid use on sleep among individuals with chronic pain has been mixed. This study aimed to determine if pain intensity moderates the association between opioid use and insomnia symptoms among adults with comorbid symptoms of insomnia and chronic widespread pain.

METHODS: Participants (N = 144; 95% female; mean age = 51.6, SD = 11.4) completed assessments of insomnia symptoms, pain and use of sleep/pain medication. Multiple regression was used to determine if pain intensity moderates the association between opioid use (yes/no) sleep onset latency (SOL), wake after sleep onset (WASO), sleep quality, or time in bed. Analyses controlled for gender, symptoms of sleep apnea, symptoms of depression, use of sleep medication (yes/no), and use of non-opioid pain medication (yes/no).

RESULTS: Stronger pain intensity was associated with longer self-reported WASO and worse sleep quality, independent of opioid use. Conversely, opioid use was associated with longer time in bed, independent of pain intensity. Opioid use and pain intensity interacted in the prediction of SOL, such that opioid use (vs. non-use) was associated with longer SOL in the context of mild but not moderate to severe pain intensity.

CONCLUSIONS: Opioid use was associated with more difficulty falling asleep among adults with chronic pain; however, this cross-sectional effect was only significant among those reporting lower pain intensity. Authors speculate that this effect is masked among those with severe pain because the pain-related sleep debt they acquire throughout the night then facilitates sleep onset the next day.

OTHER RESEARCH OF INTEREST

**Psychometric properties of the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder based on veterans' period of service.**

Bhattarai JJ¹, Oehlert ME², Weber DK².

Psychol Serv. 2018 Sep 27. doi: 10.1037/ser0000285. PMID: 30265072. [Epub ahead of print]

The Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (M-PTSD) is a 35-item screening instrument for combat-related PTSD (Keane, Caddell, & Taylor, 1988) that has been normed largely on veterans from the Vietnam era. Research on its psychometric properties with veterans across different periods of service (POS) remains limited; however, this is an important research endeavor because of the uniqueness in experiences across eras which may influence PTSD rates, symptom expression/complaints, and treatment completion/outcomes. In this study, our objective was to examine the instrument's properties, replicating Keane et al.'s (1988) methodologies, with veterans from World War II, Korean, Vietnam, post-Vietnam, and Persian Gulf (pre-and post-9/11) eras. This retrospective cohort study involved the examination of medical records of 29,280 veterans receiving care across Veterans Affairs medical outpatient centers nationwide. The data revealed significant differences across POS in terms of M-PTSD total scores, \( F(4, 29,275) = 55.01, p = .000 \); therefore, analyses were conducted with the entire sample and with each POS. The instrument demonstrated high internal consistency with our sample (\( \alpha = .92 \)) and across POS (.91 to .92). Receiver operating characteristic curves identified cut-scores ranging from 86 to 112 across the POS with acceptable-to-good sensitivity (68% to 81%) and fair-to-acceptable specificity (61% to 70%), with lower scores among World War II and Korean era veterans compared with veterans from more recent conflicts. In terms of clinical implications, the M-PTSD is a brief, easily accessible, valuable screening tool for combat-related PTSD in veterans across a range of POS. Future studies should consider the methodologies utilized to diagnose PTSD and how this potentially impacts the instrument's properties.
**Mental Health Impact of Homecoming Experience Among 1730 Formerly Deployed Veterans From the Vietnam War to Current Conflicts Results From the Veterans' Health Study.**

Boscarino JA1, Adams RE2, Urosevich TG3, Hoffman SN4, Kirchner HL5, Boscarino JJ6, Withey CA1, Dugan RJ1, Figley CR7.


We examined the effects of homecoming support on current mental health among 1730 deployed veterans from Vietnam, Iraq/Afghanistan, Persian Gulf, and other conflicts. The prevalence of current posttraumatic stress disorder (PTSD) was 5.4%, current depression was 8.3%, and 5.4% had suicidal thoughts in the past month. Overall, 26% of veterans had low homecoming support, which was more prevalent among Vietnam veterans (44.3%, p < 0.001). In multivariable logistic regressions, controlling for demographics, combat exposure, number of deployments, trauma history, and operational theater, low postdeployment support was associated with PTSD (odds ratio, 2.13; p = 0.032) and suicidality (odds ratio, 1.91; p < 0.030), but not depression. For suicidality, an interaction was detected for homecoming by theater status, whereby Iraq/Afghanistan veterans with lower homecoming support had a higher probability of suicidal thoughts (p = 0.002). Thus, years after deployment, lower homecoming support was associated with current PTSD and suicidality, regardless of theater and warzone exposures. For suicidality, lower support had a greater impact on Iraq/Afghanistan veterans.

**Specific PTSD symptom clusters mediate the association of military sexual trauma severity and sexual function and satisfaction in female service members/veterans.**

Blais RK1, Geiser C2, Cruz RA2.


BACKGROUND: Sexual satisfaction and function are vastly understudied in female service members/veterans (SM/Vs). Military sexual trauma (MST) is associated with poorer sexual satisfaction and function, but the mechanism through which MST relates to sexual satisfaction and function is unknown. Posttraumatic stress disorder (PTSD) is one of the most frequent diagnoses following MST, and those with poorer sexual satisfaction and function experience higher PTSD symptoms, particularly numbing and anhedonia symptom clusters. In this study, we examined which symptom clusters (re-experiencing, avoidance, negative alterations in cognition and mood [NACM], anhedonia, dysphoric and anxious arousal) mediated the relationship between MST and sexual satisfaction and function.

METHOD: Female SM/Vs (N = 1,189) completed self-report measures of MST severity (none, harassment only, assault), PTSD, sexual satisfaction, and sexual function, as well as a demographic inventory.

RESULTS: Anhedonia and dysphoric arousal fully mediated the association between assault MST and sexual satisfaction and function. NACM fully mediated the association between harassment and assault MST and sexual satisfaction. Finally, dysphoric arousal significantly mediated the association of harassment MST with sexual satisfaction and function.

LIMITATIONS: Data was cross-sectional and based on self-report.

CONCLUSIONS: The relationship between MST and sexual satisfaction and function may be mediated through specific PTSD symptom clusters. As there are no evidenced-based treatments to improve sexual satisfaction and function in female SM/Vs, additional research is needed to develop and pilot interventions. Among those with a history of MST, targeting NACM, anhedonia, and dysphoric arousal may be most effective in addressing sexual concerns.
Chronic Traumatic Encephalopathy Within an Amyotrophic Lateral Sclerosis Brain Bank Cohort. 
Walt GS1, Burris HM1, Brady CB1,2,3, Spencer KR1, Alvarez VE1,2,3,4, Huber BR1,2,3,4, Guilderson L1, Abdul Rauf N1, Collins D1, Singh T1, Mathias R1,2, Averill JG1,2,6, Walker SE1,6, Robey I1,7, McKee AC1,2,8,4,7, Kowall NW1,2,8, Stein TD1,8,4,7. 

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disorder linked to repetitive head impacts and has been associated with amyotrophic lateral sclerosis (ALS), a fatal, degenerative neuromuscular disorder. The Department of Veterans Affairs Biorepository Brain Bank (VABBB) is a tissue repository that collects antemortem disease progression data and postmortem central nervous system tissue from veterans with ALS. We set out to determine the frequency of co-morbid ALS and CTE in the VABBB cohort and to characterize the clinical, genetic, and pathological distinctions between participants with ALS only and those with both ALS and CTE (ALS+CTE). Of 155 participants, 9 (5.8%) had neuropathologically confirmed ALS+CTE. Participants with ALS+CTE were more likely to have a history of traumatic brain injury (p < 0.001), served during the first Persian Gulf War (p < 0.05), and to have more severe tau pathology within the frontal cortex and spinal cord (p < 0.05). The most common exposures to head impacts included contact sports (n = 5) and military service (n = 2). Clinically, participants with ALS+CTE were more likely to have bulbar onset ALS (p = 0.006), behavioral changes (p = 0.002), and/or mood changes (p < 0.001). Overall, compared with ALS in isolation, comorbid ALS+CTE is associated with a history of TBI and has a distinct clinical and pathological presentation.

The role of personality in patients with fibromyalgia. 
Seto A1, Han X1, Price LL2, Harvey WF1, Bannuru RR1,3, Wang C4. 

Previous studies suggest personality, the multifaceted characteristics underlying a person’s affect, cognition, and behavior, may influence fibromyalgia. We examined associations among personality, fibromyalgia impact, and health-related outcomes in patients with fibromyalgia. We further tested whether anxiety and depression mediated the effect of personality on fibromyalgia impact. We performed a secondary analysis using baseline data from a randomized trial on fibromyalgia. Personality was assessed using the NEO-Five Factor Inventory 3. Fibromyalgia impact was evaluated using the revised Fibromyalgia Impact Questionnaire (FIQR). We also measured symptom severity, anxiety, depression, stress, quality of life, social support, self-efficacy, outcome expectations, and mindfulness. Multivariable linear regression was performed to evaluate each association. Mediation analysis assessed whether anxiety and depression mediated the relationship between personality and FIQR. There were 92 participants, 95% female, mean age 52 years, body mass index (BMI) 30 kg/m², 52% white, and mean duration of body pain 14 years. Higher neuroticism was significantly associated with higher FIQR (P = 0.002) and symptom severity (P = 0.008), as well as higher levels of anxiety, depression and stress, worse mental component quality of life, and lower self-efficacy, mindfulness, and social support. Higher conscientiousness and extraversion were associated with better psychological health and health-related outcomes. The effect of neuroticism on fibromyalgia impact was mediated by anxiety and depression. Personality was associated with fibromyalgia impact and a variety of health outcomes. Identifying the factors that influence fibromyalgia will help us better understand the condition and provide insight for more effective treatment.