GULF WAR ILLNESS

Behavioral, cellular and molecular maladaptations covary with exposure to pyridostigmine bromide in a rat model of gulf war illness pain.

Cooper BY[1], Flunker LD[2], Johnson RD[3], Nutter TJ[4].

Toxicol Appl Pharmacol. **2018 Aug 1**;352:119-131. doi: 10.1016/j.taap.2018.05.023. PMID: 29803855. Epub 2018 May 24.

Many veterans of Operation Desert Storm (ODS) struggle with the chronic pain of Gulf War Illness (GWI). Exposure to insecticides and pyridostigmine bromide (PB) have been implicated in the etiology of this multisymptom disease. We examined the influence of 3 (DEET (N,N-diethyl-meta-toluamide), permethrin, chlorpyrifos) or 4 GW agents (DEET, permethrin, chlorpyrifos, pyridostigmine bromide (PB)) on the post-exposure ambulatory and resting behaviors of rats. In three independent studies, rats that were exposed to all 4 agents consistently developed both immediate and delayed ambulatory deficits that persisted at least 16 weeks after exposures had ceased. Rats exposed to a 3 agent protocol (PB excluded) did not develop any ambulatory deficits. Cellular and molecular studies on nociceptors harvested from 16WP (weeks post-exposure) rats indicated that vascular nociceptor $Na_v1.9$ mediated currents were chronically potentiated following the 4 agent protocol but not following the 3 agent protocol. Muscarinic linkages to muscle nociceptor TRPA1 were also potentiated in the 4 agent but not the 3 agent, PB excluded, protocol. Although K_v7 activity changes diverged from the behavioral data, a K_v7 opener, retigabine, transiently reversed ambulation deficits. We concluded that PB played a critical role in the development of pain-like signs in a GWI rat model and that shifts in $Na_v1.9$ and TRPA1 activity were critical to the expression of these pain behaviors.

CHRONIC FATIGUE SYNDROME

Association between cytokines and psychiatric symptoms in chronic fatigue syndrome and healthy controls.

Groven N[1], Fors EA[2], Iversen VC[1,3], White LR[4, 5], Reitan SK[1,6].

Nord J Psychiatry. **2018 Jul 31**:1-5. doi: 10.1080/08039488.2018.1493747. PMID: 30063870. [Epub ahead of print]

PURPOSE: The reports regarding the status of the immune system in patients with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) have been inconclusive. We approached this question by comparing a strictly defined group of CFS/ME outpatients to healthy control individuals, and thereafter studied cytokines in subgroups with various psychiatric symptoms.

MATERIALS AND METHODS: Twenty patients diagnosed with CFS/ME according to the Fukuda criteria and 20 age- and sex-matched healthy controls were enrolled in the study. Plasma was analysed by ELISA for levels of the cytokines TNF-α, IL-4, IL-6 and IL-10. Participants also answered questionnaires regarding health in general, and psychiatric symptoms in detail.

RESULTS: Increased plasma levels of TNF-α in CFS/ME patients almost reached significance compared to healthy controls ($p = .056$). When studying the CFS/ME and control groups separately, there was a significant correlation between TNF-α and The Hospital Anxiety and Depression Scale (HADS) depressive symptoms in controls only, not in the CFS/ME group. A correlation between IL-10 and psychoticism was found in both groups, whereas the correlation for somatisation was seen only in the CFS/ME group. When looking at the total population, there was a significant correlation between TNF-α and both the HADS depressive symptoms and the SCL-90-R cluster somatisation. Also, there was a significant association between IL-10 and the SCL-90-R cluster somatisation when analyzing the cohort (patients and controls together).

CONCLUSIONS: These findings indicate that immune activity in CFS/ME patients deviates from that of healthy controls, which implies potential pathogenic mechanisms and possible therapeutic approaches to CFS/ME. More comprehensive studies should be carried out on defined CFS/ME subgroups.

CHRONIC FATIGUE SYNDROME (Continued)

Dimensional Personality Assessment among a Chronic Fatigue Syndrome (CFS) sample with Personality Inventory for DSM-5 (PID-5).

Calvo N[1], Pueyo N[2], Gutiérrez F[3], Ferrer M[1], Castro-Marrero J[4], Alegre J[4], Casas M[1], Ramos Quiroga JA[5], Sáez-Francàs N[6].

Actas Esp Psiquiatr. **2018 Jul**;46(4):125-32. PMID: 30079926. Epub 2018 Jul 1.

INTRODUCTION: Personality Disorders (PD) are highly prevalent among Chronic Fatigue Syndrome (CFS) patients, but studies based on the DSM-5 are still scarce. Validated instruments have not yet been specifically used in CFS patients. Therefore, our aim was to analyze the differences in personality facets and domains profiles among CFS patients with and without a PD using the Personality Inventory for DSM-5 (PID-5). Additionally, we analyzed the ability of this instrument to predict PD in a sample of CFS patients. This instrument is validated for PDs, but not for CFS.

METHODS: All of the 84 CFS patients were evaluated through a clinical interview and underwent psychopathological evaluation with the SCID I and SCID II. Dimensional personality facets and domains were evaluated with the PID-5, according to DSM-5.

RESULTS: In our sample, 54 (64%) of the patients fulfilled the criteria of a PD. The most significant facets in CFS with PD in comparison to those patients without a PD were Separation Insecurity, Perseveration, Withdrawal, Depressivity, Rigid Perfectionism, Unusual Beliefs and Experiences. Negative Affectivity and Detachment were the two significant domains in CFS-PD patients. In the regression analyses, only Detachment and Rigid Perfectionism constituted a prognostic factor leading to high probability of an endorsed PD.

CONCLUSSION. According to these results, the PID-5 domains and facets could be adequate and useful to differentiate between PD and non-PD patients in clinical samples and suggest a more frequent dimensional personality profile in CFS patients.

HEADACHE and MIGRAINE

Fibromyalgia in migraine: a retrospective cohort study.

Whealy M[1], Nanda S[2], Vincent A[2], Mandrekar J[3], Cutrer FM[4].

J Headache Pain. **2018 Jul 31**;19(1):61. doi: 10.1186/s10194-018-0892-9. PMID: 30066109.

BACKGROUND: Migraine is a common and disabling disorder. Fibromyalgia has been shown to be commonly comorbid in patients with migraine and can intensify disability. The aim of this study was to determine if patients with co-morbid fibromyalgia and migraine report more depressive symptoms, have more headache related disability, or report higher intensity of headache as compared to patients with migraine only. Cases of comorbid fibromyalgia and migraine were identified using a prospectively maintained headache database at Mayo Clinic Rochester. One-hundred and fifty seven cases and 471 controls were identified using this database and the Mayo Clinic electronic medical record.

FINDINGS: Depressive symptoms as assessed by PHQ-9, intensity of headache, and migraine related disability as assessed by MIDAS were primary measures used to compare migraine patients with comorbid fibromyalgia versus those without. Patients with comorbid fibromyalgia reported significantly higher PHQ-9 scores (OR 1.08, $p < .0001$) and headache intensity scores (OR 1.149, $p = .007$). There was no significant difference in migraine related disability (OR 1.002, $p = .075$). Patients with fibromyalgia were more likely to score in a higher category of depression severity (OR 1.467, $p < .0001$) and more likely to score in a higher category of migraine related disability (OR 1.23, $p = .004$).

CONCLUSION: Patients with comorbid fibromyalgia and migraine report more depressive symptoms, higher headache intensity, and are more likely to have severe headache related disability as compared to controls without fibromyalgia. Clinicians who care for patients with migraine may consider screening for comorbid fibromyalgia particularly in patients with moderate to severe depressive symptoms, high headache intensity and/or high headache related disability. This is the first matched study to look at these characteristics, and it replicates previous findings from unmatched studies.

HEADACHE and MIGRAINE (Continued)

RVCL-S and CADASIL display distinct impaired vascular function.

de Boer I[1], Stam AH[1], Buntinx L[1], Zielman R[1], van der Steen I[1], van den Maagdenberg AMJM[1], de Koning EJP[1], Ferrari MD[1], de Hoon JN[1], Terwindt GM[2].

Neurology. **2018 Aug 3**. pii: 10.1212/WNL.0000000000006119. doi: 10.1212/WNL.0000000000006119. PMID: 30076273. [Epub ahead of print]

OBJECTIVE: We aimed to evaluate the role of endothelial-dependent and endothelial-independent vascular reactivity in retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), both cerebral small vessel diseases are considered models for stroke, vascular dementia, and migraine.

METHODS: RVCL-S (n = 18) and CADASIL (n = 23) participants with *TREX1* and *NOTCH3* mutations, respectively, were compared with controls matched for age, body mass index, and sex (n = 26). Endothelial function was evaluated by flow-mediated vasodilatation, and endothelial-independent vascular reactivity (i.e., vascular smooth muscle cell function) was assessed by dermal blood flow response to capsaicin application.

RESULTS: Flow-mediated vasodilatation was decreased in participants with RVCL-S compared with controls (2.32% ± 3.83% vs 5.76% ± 3.07% change in diameter, $p = 0.023$) but normal in participants with CADASIL. Vascular smooth muscle cell function was reduced in participants with CADASIL compared with controls (maximal dermal blood flow increase at 40 minutes after capsaicin: 1.38 ± 0.88 vs 2.22 ± 1.20 arbitrary units, $p = 0.010$) but normal in participants with RVCL-S.

CONCLUSIONS: We identified endothelial dysfunction in RVCL-S and confirmed impaired vascular smooth muscle cell relaxation in CADASIL. Our findings may prove to be biomarkers for disease progression in both monogenic cerebral small vessel diseases and improve mechanistic insight in their pathophysiology. This may help in understanding common neurovascular disorders, including stroke, dementia, and migraine.

Structured Clinical Documentation to Improve Quality and Support Practice-Based Research in Headache.

Meyers S[1], Claire Simon K[1], Bergman-Bock S[1], Campanella F[1], Marcus R[1], Mark A[1], Freedom T[1], Rubin S[1], Semenov I[1], Lai R[2], Hillman L[2], Tideman S[1], Pham A[1], Frigerio R[1], Maraganore DM[1].

Headache. **2018 Aug 1**. doi: 10.1111/head.13348. PMID: 30066412. [Epub ahead of print]

OBJECTIVE: To use the electronic medical record (EMR) to optimize patient care, facilitate documentation, and support quality improvement and practice-based research, in a headache specialty clinic.

BACKGROUND: Many physicians enter data into the EMR as unstructured free text and not as discrete data. This makes it challenging to use data for quality improvement or research initiatives.

METHODS: We describe the process of building a customized structured clinical documentation support toolkit, specific for patients seen in a headache specialty clinic. The content was developed through frequent physician meetings to reach consensus on elements that define clinical Best Practices. Tasks were assigned to the care team and data mapped to the progress note.

RESULTS: The toolkit collects hundreds of fields of discrete, standardized data. Auto scored and interpreted score tests include the Generalized Anxiety Disorder 7-item, Center for Epidemiology Studies Depression Scale, Migraine Disability Assessment questionnaire, Insomnia Sleep Index, and Migraine-Specific Quality of Life. We have developed Best Practice Advisories (BPA) and other clinical documentation support tools that alert physicians, when appropriate. As of April 1, 2018, we have used the toolkits at 4346 initial patient visits. We provide screenshots of our toolkits, details of data fields collected, and diagnoses of patients at the initial visit.

CONCLUSIONS: The EMR can be used to effectively structure and standardize headache clinic visits for quality improvement and practice-based research. We are sharing our proprietary toolkit with other clinics as part of the Neurology Practice-Based Research Network. These tools are also facilitating clinical research enrollment and a pragmatic trial of comparative effectiveness at the point-of-care among migraine patients.

HEADACHE and MIGRAINE (Continued)

Associations between adherence to dietary approaches to stop hypertension (DASH) diet and migraine headache severity and duration among women.

Mirzababaei A[1], Khorsha F[1], Togha M[2,3], Yekaninejad MS[4], Okhovat AA[5], Mirzaei K[1].

Nutr Neurosci. **2018 Jul 31**:1-8. doi: 10.1080/1028415X.2018.1503848. PMID: 30064351. [Epub ahead of print]

PURPOSE/INTRODUCTION: Migraine is a common disorder, with attacks causing neurological dysfunction and pain. Many foods are involved in reducing the severity of migraine attacks. This study aimed to assess the effects that adhering to the Dietary approaches to stop hypertension (DASH) diet had on headache severity and duration among women suffering from migraine.

METHODS AND MATERIALS: Two hundred and sixty-six women (18-45 years) were enrolled after being referred to a headache clinic for the first time. Dietary intake was assessed daily using a Food Frequency Questionnaire. Anthropometric measurements were assessed for all cases, as well as headache duration of each attack; Visual Analog Scale and Migraine Disability Assessment questionnaires were evaluated by a neurologist.

RESULTS: The mean age, weight, and height of the study participants were 34.32 (SD 7.86) years, 69.41 (13.02) kg, and 161 (0.05) cm, respectively. The results of analysis in the crude model showed that individuals with the greatest adherence to the DASH diet displayed a 30% lower prevalence in severe headaches, compared to those with the lowest adherence (OR=0.70, 95%CI=0.49-0.99, P<0.05). Also, after controlling for potential confounders, subjects in the highest quartile of DASH diet adherence were 46% less likely to have severe headaches, and also saw a 36% lower occurrence of moderate headaches, compared to those in the bottom quartile (OR=0.54, 95%CI=0.35-0.83, P<0.005 and OR=0.64, 95%CI=0.44-0.95, P<0.005, respectively). These results showed a significant positive correlation between adherence to DASH diets and lower rates of mean headache duration for each attack in the last month (β=-1.49, CI=0.21-2.7, P=0.02).

CONCLUSION: This study showed that the DASH diet is associated with lower headache severity and duration in migraine patients.

CHRONIC PAIN

High levels of cerebrospinal fluid chemokines point to the presence of neuroinflammation in peripheral neuropathic pain: a cross-sectional study of 2 cohorts of patients compared with healthy controls.

Bäckryd E[1], Lind AL, Thulin M, Larsson A, Gerdle B, Gordh T.

Pain. **2017 Dec**;158(12):2487-2495. doi: 10.1097/j.pain.0000000000001061. PMID: 28930774. PMCID: PMC5690569.

Animal models suggest that chemokines are important mediators in the pathophysiology of neuropathic pain. Indeed, these substances have been called "gliotransmitters," a term that illustrates the close interplay between glial cells and neurons in the context of neuroinflammation and pain. However, evidence in humans is scarce. The aim of the study was to determine a comprehensive cerebrospinal fluid (CSF) inflammatory profile of patients with neuropathic pain. Our hypothesis was that we would thereby find indications of a postulated on-going process of central neuroinflammation. Samples of CSF were collected from 2 cohorts of patients with neuropathic pain (n = 11 and n = 16, respectively) and healthy control subjects (n = 11). The samples were analyzed with a multiplex proximity extension assay in which 92 inflammation-related proteins were measured simultaneously (Proseek Multiplex Inflammation I; Olink Bioscience, Uppsala, Sweden). Univariate testing with control of false discovery rate, as well as orthogonal partial least squares discriminant analysis, were used for statistical analyses. Levels of chemokines CXCL6, CXCL10, CCL8, CCL11, CCL23 in CSF, as well as protein LAPTGF-beta-1, were significantly higher in both neuropathic pain cohorts compared with healthy controls, pointing to neuroinflammation in patients. These 6 proteins were also major results in a recent similar study in patients with fibromyalgia. The findings need to be confirmed in larger cohorts, and the question of causality remains to be settled. Because it has been suggested that prevalent comorbidities to chronic pain (eg, depression, anxiety, poor sleep, and tiredness) also are associated with neuroinflammation, it will be important to determine whether neuroinflammation is a common mediator.

CHRONIC PAIN (Continued)

Effects of Osteoarthritis Pain, and Concurrent Insomnia and Depression on Health Care Use in a Primary Care Population of Older Adults.

Liu M[1,2,3], McCurry SM[4,5], Belza B[2], Dobra A[2,6,7], Buchanan DT[2], Vitiello MV[2,5], Von Korff M[8].

Arthritis Care Res (Hoboken). **2018 Aug 1**. doi: 10.1002/acr.23695. PMID: 30067892. [Epub ahead of print]

OBJECTIVE: To examine independent and combined effects of pain with concurrent insomnia and depression symptoms on health care use (HCU) in older adults with osteoarthritis (OA).

METHODS: Participants were Group Health Cooperative (GHC) patients with a primary diagnosis of OA (N = 2,976). We used survey data on pain (Graded Chronic Pain Scale), insomnia (Insomnia Severity Index), and depression (Patient Health Questionnaire-8), and HCU extracted from GHC electronic health records (office visits, length of stay [LOS], outpatient and inpatient costs, and hip/knee replacement) for three years after the survey. Negative binomial, logistic, and generalized linear models were employed to assess HCU predictors.

RESULTS: About 34% and 29% of participants presented at least sub-clinical insomnia and at least sub-clinical depression symptoms, respectively, in addition to moderate to severe pain. Pain had the largest independent effects on increasing all types of HCU, followed by depression (moderate effects) on increased office visits, LOS, outpatient and inpatient costs, and insomnia (mild effects) on decreased LOS. No synergistic effects were found on HCU among the three symptoms. Combined effects of pain + insomnia, and pain + depression were significant for all types of HCU and increased greatly with increasing insomnia and depression severity except for hip/knee replacement.

CONCLUSION: Pain is the main driver for HCU in OA. Insomnia and depression jointly increased diverse types of HCU in addition to pain and these combined effects increased greatly with increasing insomnia and depression severity. These findings indicate the important role that concurrent symptomatic conditions may play in increasing HCU.

Discrepancies in sleep diary and actigraphy assessments in adults with fibromyalgia: Associations with opioid dose and age.

Curtis AF[1], Miller MB[1], Boissoneault J[2], Robinson M[2], Staud R[3], Berry RB[3], McCrae CS[1].

J Sleep Res. **2018 Jul 31**:e12746. doi: 10.1111/jsr.12746. PMID: 30062746. [Epub ahead of print]

Sleep diary and actigraphy assessments of insomnia symptoms in patients with fibromyalgia (FM) are often discrepant. We examined whether opioid dose and age interact in predicting magnitude or direction of discrepancies. Participants (N = 199, M = 51.5 years, SD = 11.7) with FM and insomnia completed 14 days of diaries and actigraphy. Multiple regressions determined whether average opioid dose and its interaction with age predicted magnitude or direction of diary/actigraphy discrepancies in sleep onset latency (SOL), wake after sleep onset (WASO) and sleep efficiency (SE), controlling for sex, use of sleep medication, evening pain and total sleep time. Higher opioid dose predicted greater magnitude of discrepancy in SOL and SE. Opioid dose interacted with age to predict direction but not magnitude of discrepancy in SOL and SE. Specifically, higher opioid use was associated with better subjective (shorter SOL, higher SE) than objective reports of sleep among younger adults, and longer subjective than objectively measured SOL among older adults. Opioid dose did not predict magnitude or direction of WASO discrepancies. In FM, a higher opioid dose increases diary/actigraphy SOL and SE discrepancies, and direction of discrepancies may depend on age. We speculate that increased opioid use combined with age-related factors, such as slow wave sleep disruption, increased awakenings and/or cognitive decline, may impact perceived sleep.

OTHER RESEARCH OF INTEREST

Mental and Physical Health Conditions in US Combat Veterans: Results From the National Health and Resilience in Veterans Study.

Thomas MM[1], Harpaz-Rotem I[2,3], Tsai J[2,4], Southwick SM[2,3], Pietrzak RH[5,2,3].

Prim Care Companion CNS Disord. **2017 Jun 22**;19(3). doi: 10.4088/PCC.17m02118. PMID: 28657698.

Objective: To identify sociodemographic and military characteristics of combat-exposed and non-combat-exposed veterans in the United States and to compare rates of mental and physical health conditions in these populations.

Methods: Data were analyzed from the National Health and Resilience in Veterans Study (NHRVS), a contemporary, nationally representative survey of 1,480 US veterans conducted September-October 2013. Poststratification weights were applied to analyses to permit generalizability of results to the US veteran population. Outcomes measured included lifetime and current psychiatric disorders and physical health conditions.

Results: A total 38% of US veterans reported being exposed to combat. Compared to noncombat veterans, combat veterans were younger, had greater household income, and served a greater number of years in the military; were more likely to be male, to have served in the Marine Corps, and to use the Veterans Affairs Healthcare System as their main source of health care; and reported a greater number of lifetime potentially traumatic events. After adjustment for these sociodemographic and military differences, combat veterans were more than 3 times as likely as noncombat veterans to screen positive for lifetime posttraumatic stress disorder (PTSD) and more than twice as likely for current PTSD and had 82% greater odds of screening positive for current generalized anxiety disorder. After additionally controlling for lifetime diagnoses of PTSD and depression, alcohol or drug use disorder, and nicotine dependence, combat veterans had 68% greater odds of having attempted suicide and 85% and 38% greater odds of being diagnosed with a stroke and chronic pain, respectively. Younger combat veterans were more likely than older combat veterans to screen positive for lifetime (30.6% vs 10.1%) and current PTSD (19.2% vs 4.9%) and suicidal ideation (18.6% vs 6.9%) and to have been diagnosed with migraine headaches (12.8% vs 2.1%), while older combat veterans were more likely than younger combat veterans to report having been diagnosed with heart disease (19.2% vs 2.6%) and heart attack (13.9% vs 2.5%).

Conclusions: Compared to noncombat veterans in the United States, combat veterans have elevated rates of PTSD, suicide attempt, stroke, and chronic pain independent of other sociodemographic, military, and mental health factors. Younger combat veterans have elevated rates of PTSD, suicidal ideation, and migraine headaches, while older combat veterans have elevated rates of heart disease and heart attack. These results characterize the population-based burden of mental and physical health conditions in combat veterans. They further underscore the importance of age- and condition-sensitive screening, monitoring, and treatment efforts in this population.

Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease.

Da Mesquita S[1,2], Louveau A[3,4], Vaccari A[5,6], Smirnov I[3,4], Cornelison RC[6], Kingsmore KM[6], Contarino C[3,4,7], Onengut-Gumuscu S[8], Farber E[8], Raper D[3,4,9], Viar KE[3,4], Powell RD[3,4], Baker W[3,4], Dabhi N[3,4], Bai R[3,4], Cao R[6], Hu S[6], Rich SS[8], Munson JM[6,10], Lopes MB[11], Overall CC[3,4], Acton ST[5,6], Kipnis J[12,13].

Nature. **2018 Jul 25**. doi: 10.1038/s41586-018-0368-8. PMID: 30046111. [Epub ahead of print]

Ageing is a major risk factor for many neurological pathologies, but its mechanisms remain unclear. Unlike other tissues, the parenchyma of the central nervous system (CNS) lacks lymphatic vasculature and waste products are removed partly through a paravascular route. (Re)discovery and characterization of meningeal lymphatic vessels has prompted an assessment of their role in waste clearance from the CNS. Here we show that meningeal lymphatic vessels drain macromolecules from the CNS (cerebrospinal and interstitial fluids) into the cervical lymph nodes in mice. Impairment of meningeal lymphatic function slows paravascular influx of macromolecules into the brain and efflux of macromolecules from the interstitial fluid, and induces cognitive impairment in mice. Treatment of aged mice with vascular endothelial growth factor C enhances meningeal lymphatic drainage of macromolecules from the cerebrospinal fluid, improving brain perfusion and learning and memory performance. Disruption of meningeal lymphatic vessels in transgenic mouse models of Alzheimer's disease promotes amyloid-β deposition in the meninges, which resembles human meningeal pathology, and aggravates parenchymal amyloid-β accumulation. Meningeal lymphatic dysfunction may be an aggravating factor in Alzheimer's disease pathology and in age-associated cognitive decline. Thus, augmentation of meningeal lymphatic function might be a promising therapeutic target for preventing or delaying age-associated neurological diseases.

OTHER RESEARCH OF INTEREST (Continued)

Mirtazapine for fibromyalgia in adults.

Welsch P[1], Bernardy K, Derry S, Moore RA, Häuser W.

Cochrane Database Syst Rev. **2018 Aug 6**;8:CD012708. doi: 10.1002/14651858.CD012708.pub2. [Epub ahead of print]

BACKGROUND: Fibromyalgia is a clinically defined chronic condition of unknown etiology characterised by chronic widespread pain, sleep disturbance, cognitive dysfunction, and fatigue. Many patients report high disability levels and poor quality of life. Drug therapy aims to reduce key symptoms, especially pain, and improve quality of life. The tetracyclic antidepressant, mirtazapine, may help by increasing serotonin and noradrenaline in the central nervous system (CNS).

OBJECTIVES: To assess the efficacy, tolerability and safety of the tetracyclic antidepressant, mirtazapine, compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, SCOPUS, the US National Institutes of Health, and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials, and examined reference lists of reviewed articles, to 9 July 2018.

SELECTION CRITERIA: Randomised controlled trials (RCTs) of any formulation of mirtazapine against placebo, or any other active treatment of fibromyalgia, in adults.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted study characteristics, outcomes of efficacy, tolerability and safety, examined issues of study quality, and assessed risk of bias, resolving discrepancies by discussion. Primary outcomes were participant-reported pain relief (at least 50% or 30% pain reduction), Patient Global Impression of Change (PGIC; much or very much improved), safety (serious adverse events), and tolerability (adverse event withdrawal). Other outcomes were health-related quality of life (HRQoL) improved by 20% or more, fatigue, sleep problems, mean pain intensity, negative mood and particular adverse events. We used a random-effects model to calculate risk difference (RD), standardised mean difference (SMD), and numbers needed to treat. We assessed the evidence using GRADE and created a 'Summary of findings' table.

MAIN RESULTS: Three studies with 606 participants compared mirtazapine with placebo (but not other drugs) over seven to 13 weeks. Two studies were at unclear or high risk of bias in six or seven of eight domains. We judged the evidence for all outcomes to be low- or very low-quality because of poor study quality, indirectness, imprecision, risk of publication bias, and sometimes low numbers of events. There was no difference between mirtazapine and placebo for any primary outcome: participant-reported pain relief of 50% or greater (22% versus 16%; RD 0.05, 95% confidence interval (CI) -0.01 to 0.12; three studies with 591 participants; low-quality evidence); no data available for PGIC; only a single serious adverse event for evaluation of safety (RD -0.00, 95% CI -0.01 to 0.02; three studies with 606 participants; very low-quality evidence); and tolerability as frequency of dropouts due to adverse events (3% versus 2%; RD 0.00, 95% CI -0.02 to 0.03; three studies with 606 participants; low-quality evidence).Mirtazapine showed a clinically-relevant benefit compared to placebo for some secondary outcomes: participant-reported pain relief of 30% or greater (47% versus 34%; RD 0.13, 95% CI 0.05 to 0.21; number needed to treat for an additional beneficial outcome (NNTB) 8, 95% CI 5 to 20; three studies with 591 participants; low-quality evidence); participant-reported mean pain intensity (SMD -0.29, 95% CI -0.46 to -0.13; three studies with 591 participants; low-quality evidence); and participant-reported sleep problems (SMD -0.23, 95% CI -0.39 to -0.06; three studies with 573 participants; low-quality evidence). There was no benefit for improvement of participant-reported improvement of HRQoL of 20% or greater (58% versus 50%; RD 0.08, 95% CI -0.01 to 0.16; three studies with 586 participants; low-quality evidence); participant-reported fatigue (SMD -0.02, 95% CI -0.19 to 0.16; two studies with 533 participants; low-quality evidence); participant-reported negative mood (SMD -0.67, 95% CI -1.44 to 0.10; three studies with 588 participants; low-quality evidence); or withdrawals due to lack of efficacy (1.5% versus 0.1%; RD 0.01, 95% CI -0.01 to 0.02; three studies with 605 participants; very low-quality evidence).There was no difference between mirtazapine and placebo for participants reporting any adverse event (76% versus 59%; RD 0.12, 95 CI -0.01 to 0.26; three studies with 606 participants; low-quality evidence). There was a clinically-relevant harm with mirtazapine compared to placebo: in the number of participants with somnolence (42% versus 14%; RD 0.24, 95% CI 0.18 to 0.30; number needed to treat for an additional harmful outcome (NNTH) 5, 95% CI 3 to 6; three studies with 606 participants; low-quality evidence); weight gain (19% versus 1%; RD 0.17, 95% CI 0.11 to 0.23; NNTH 6, 95% CI 5 to 10; three studies with 606 participants; low-quality evidence); and elevated alanine aminotransferase (13% versus 2%; RD 0.13, 95% CI 0.04 to 0.22; NNTH 8, 95% CI 5 to 25; two studies with 566 participants; low-quality evidence).

AUTHORS' CONCLUSIONS: Studies demonstrated no benefit of mirtazapine over placebo for pain relief of 50% or greater, PGIC, improvement of HRQoL of 20% or greater, or reduction of fatigue or negative mood. Clinically-relevant benefits were shown for pain relief of 30% or greater, reduction of mean pain intensity, and sleep problems. Somnolence, weight gain, and elevated alanine aminotransferase were more frequent with mirtazapine than placebo. The quality of evidence was low or very low, with two of three studies of questionable quality and issues over indirectness and risk of publication bias. On balance, any potential benefits of mirtazapine in fibromyalgia were outweighed by its potential harms, though, a small minority of people with fibromyalgia might experience substantial symptom relief without clinically-relevant adverse events.

OTHER RESEARCH OF INTEREST (Continued)

National Academy of Medicine Launches Action Collaborative to Counter Opioid Epidemic; Public-Private Partnership Will Coordinate Initiatives Across Sectors to Drive Collective Solutions

National Academies of Sciences, Engineering, and Medicine, **July 31, 2018**, Washington, D.C., News Release.

In recognition of the need for a national coordinated and collective response to the epidemic of opioid addiction in the U.S., the National Academy of Medicine (NAM), in partnership with the Aspen Institute, launched a public-private partnership made up of more than 35 organizations representing federal, state, and local governments, health systems, associations and provider groups, health education and accrediting institutions, pharmacies, payers, industry, nonprofits, and academia. This partnership -- the NAM Action Collaborative on Countering the U.S. Opioid Epidemic -- is committed to sharing knowledge, aligning ongoing initiatives, and addressing complex challenges that require a shared response from public and private actors. The collaborative will establish shared priorities, identify unmet needs, and develop and disseminate evidence-based, multi-sector solutions to reduce rates of opioid misuse and improve outcomes for individuals, families, and communities affected by addiction

“Since it was declared a public health emergency in October 2017, so many organizations are working around the clock to reverse the opioid epidemic, yet progress has been slow,” said Victor J. Dzau, NAM president and chair of the collaborative. “The problem is clearly not absence of will, but insufficient alignment and coordination across sectors. The complex drivers of the opioid epidemic make it impossible for any single organization or professional sector to make a significant impact on its own. This one-of-a-kind public-private partnership will bring stakeholders from government, academia, the health care industry, health education, and communities impacted by addiction under the same roof to build collective solutions and accelerate the pace of progress.

Since 1999, the number of opioid-related deaths -- from both prescription opioids and illegal drugs including heroin, fentanyl, and carfentanil -- has quadrupled. Driven in large part by the opioid epidemic, drug overdose is the leading cause of accidental death in the U.S., resulting in 170 deaths every day. Addiction and overdose not only destroy individual lives, but erode the health and prosperity of entire families and communities. The economic toll is significant; according to the President’s Council of Economic Advisers, the opioid crisis cost $504 billion in 2015, or 2.8 percent of gross domestic product.

The collaborative will focus on areas such as the over-prescription of opioids for treatment of pain, where progress requires the involvement of clinicians, researchers, and regulators; inadequate health provider education and training, for which improvement depends on the commitment of educators, accrediting institutions, and specialty organizations across the health professions; and under-treatment of opioid use disorders, which requires health industry innovation and collaboration with policymakers and care providers at all levels to achieve progress.

[Link to full text of this NASEM News Release.]

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