GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics.

Nagy-Szakal D[1], Barupal DK[2], Lee B[1], Che X[1], Williams BL[1], Kahn EJR[1], Ukaigwe JE[1], Bateman L[3], Klimas NG[4,5], Komaroff AL[6], Levine S[7], Montoya JG[8], Peterson DL[9], Levin B[10], Hornig M[1], Fiehn O[11], Lipkin WI[12].

Sci Rep. **2018 Jul 3**;8(1):10056. doi: 10.1038/s41598-018-28477-9. PMID: 29968805.

The pathogenesis of ME/CFS, a disease characterized by fatigue, cognitive dysfunction, sleep disturbances, orthostatic intolerance, fever, irritable bowel syndrome (IBS), and lymphadenopathy, is poorly understood. We report biomarker discovery and topological analysis of plasma metabolomic, fecal bacterial metagenomic, and clinical data from 50 ME/CFS patients and 50 healthy controls. We confirm reports of altered plasma levels of choline, carnitine and complex lipid metabolites and demonstrate that patients with ME/CFS and IBS have increased plasma levels of ceramide. Integration of fecal metagenomic and plasma metabolomic data resulted in a stronger predictive model of ME/CFS (cross-validated AUC = 0.836) than either metagenomic (cross-validated AUC = 0.745) or metabolomic (cross-validated AUC = 0.820) analysis alone. Our findings may provide insights into the pathogenesis of ME/CFS and its subtypes and suggest pathways for the development of diagnostic and therapeutic strategies.

Intracranial compliance is associated with symptoms of orthostatic intolerance in chronic fatigue syndrome.

Finkelmeyer A[1], He J[2,3], Maclachlan L[4], Blamire AM [2], Newton JL[4].

PLoS One. **2018 Jul 3**;13(7):e0200068. doi: 10.1371/journal.pone.0200068. PMID: 29969498. eCollection 2018.

Symptoms of orthostatic intolerance (OI) are common in Chronic Fatigue Syndrome (CFS) and similar disorders. These symptoms may relate to individual differences in intracranial compliance and cerebral blood perfusion. The present study used phase-contrast, quantitative flow magnetic resonance imaging (MRI) to determine intracranial compliance based on arterial inflow, venous outflow and cerebrospinal fluid flow along the spinal canal into and out of the cranial cavity. Flow-sensitive Alternating Inversion Recovery (FAIR) Arterial Spin Labelling was used to measure cerebral blood perfusion at rest. Forty patients with CFS and 10 age and gender matched controls were scanned. Severity of symptoms of OI was determined from self-report using the Autonomic Symptom Profile. CFS patients reported significantly higher levels of OI ($p < .001$). Within the patient group, higher severity of OI symptoms were associated with lower intracranial compliance ($r = -.346$, $p = .033$) and higher resting perfusion ($r = .337$, $p = .038$). In both groups intracranial compliance was negatively correlated with cerebral perfusion. There were no significant differences between the groups in intracranial compliance or perfusion. In patients with CFS, low intracranial compliance and high resting cerebral perfusion appear to be associated with an increased severity of symptoms of OI. This may signify alterations in the ability of the cerebral vasculature to cope with changes to systemic blood pressure due to orthostatic stress, but this may not be specific to CFS.

CHRONIC FATIGUE SYNDROME (Continued)

Reduction of Glucocorticoid Receptor Function in Chronic Fatigue Syndrome.

Lynn M[1], Maclachlan L[2], Finkelmeyer A[1], Clark J[1], Locke J[3], Todryk S[3,4], Ng WF[3,5], Newton JL[3,5], Watson S[1,6].

Mediators Inflamm. **2018 Jun 10**;2018:3972104. doi: 10.1155/2018/3972104. PMCID: PMC6015684. PMID: 29983634. eCollection 2018.

Glucocorticoid receptor (GR) function may have aetiopathogenic significance in chronic fatigue syndrome (CFS), via its essential role in mediating inflammatory responses as well as in hypothalamic-pituitary-adrenal axis regulation. GR function can be estimated ex vivo by measuring dexamethasone (dex) modulation of cytokine response to lipopolysaccharide (LPS), and *in vivo* using the impact of dex on cortisol levels. This study aimed to compare the GR function between CFS (*n* = 48), primary Sjögren's syndrome (a disease group control) (*n* = 27), and sedentary healthy controls (HCs) (*n* = 20), and to investigate its relationship with clinical measures. In the GR ex vivo response assay, whole blood was diluted and incubated with LPS (to stimulate cytokine production), with or without 10 or 100 nanomolar concentrations of dex. Cytometric bead array (CBA) and flow cytometry enabled quantification of cytokine levels (TNF*α*, interleukin- (IL-) 6, and IL-10) in the supernatants. In the *in vivo* response assay, five plasma samples were taken for determination of total cortisol concentration using ELISA at half-hourly intervals on two consecutive mornings separated by ingestion of 0.5 mg of dex at 11 pm. The association of the data from the *in vivo* and ex vivo analyses with reported childhood adversity was also examined. CFS patients had reduced LPS-induced IL-6 and TNF*α* production compared to both control groups and reduced suppression of TNF*α* by the higher dose of dex compared to HCs. Cortisol levels, before or after dex, did not differ between CFS and HCs. Cortisol levels were more variable in CFS than HCs. In the combined group (CFS plus HC), cortisol concentrations positively and ex vivo GR function (determined by dex-mediated suppression of IL-10) negatively correlated with childhood adversity score. The results do not support the hypothesis that GR dysregulation is aetiopathogenic in CFS and suggest that current and future endocrine cross-sectional studies in CFS may be vulnerable to the confounding influence of childhood trauma which is likely increased by comorbid depression.

HEADACHE and MIGRAINE

Sildenafil and calcitonin gene-related peptide dilate intradural arteries: A 3T MR angiography study in healthy volunteers.

Christensen CE[1], Amin FM[1], Younis S[1], Lindberg U[2], de Koning P[3], Petersen ET[4], Paulson OB[5], Larsson HBW[2], Ashina M[1].

Cephalalgia. **2018 Jan 1**:333102418787336. doi: 10.1177/0333102418787336. PMID: 29976087. [Epub ahead of print]

Background: Sildenafil and calcitonin gene-related peptide are vasoactive substances that induce migraine attacks in patients. The intradural arteries are thought to be involved, but these have never been examined in vivo. Sildenafil is the only migraine-inducing compound for which cephalic, extracranial artery dilation is not reported. Here, we investigate the effects of sildenafil and calcitonin gene-related peptide on the extracranial and intradural parts of the middle meningeal artery.

Methods: In a double-blind, randomized, three-way crossover, placebo-controlled head-to-head comparison study, MR-angiography was recorded in healthy volunteers at baseline and twice after study drug (sildenafil/ calcitonin gene-related peptide/saline) administration. Circumferences of extracranial and intradural middle meningeal artery segments were measured using semi-automated analysis software. The area under the curve for circumference change was compared using paired t-tests between study days.

Results: Twelve healthy volunteers completed the study. The area under the curve$_{\text{Baseline-120min}}$ was significantly larger on both the sildenafil and the calcitonin gene-related peptide day in the intradural middle meningeal artery (calcitonin gene-related peptide, p = 0.013; sildenafil, p = 0.027) and the extracranial middle meningeal artery (calcitonin gene-related peptide, p = 0.0003; sildenafil, p = 0.021), compared to placebo. Peak intradural middle meningeal artery dilation was 9.9% (95% CI [2.9-16.9]) after sildenafil (T_{30min}) and 12.5% (95% CI [8.1-16.8]) after calcitonin gene-related peptide (T_{30min}). Peak dilation of the extracranial middle meningeal artery after calcitonin gene-related peptide (T_{30min}) was 15.7% (95% CI [11.2-20.1]) and 18.9% (95% CI [12.8-24.9]) after sildenafil (T_{120min}).

Conclusion: An important novel finding is that both sildenafil and calcitonin gene-related peptide dilate intradural arteries, supporting the notion that all known pharmacological migraine triggers dilate cephalic vessels. We suggest that intradural artery dilation is associated with headache induced by calcitonin gene-related peptide and sildenafil.

HEADACHE and MIGRAINE (Continued)

Association of white matter hyperintensities with migraine features and prognosis.

Xie H[1], Zhang Q[1,2], Huo K[1], Liu R[1], Jian ZJ[1], Bian YT[3], Li GL[4], Zhu D[1], Zhang LH[1], Yang J[3], Luo GG[5].

BMC Neurol. **2018 Jul 2**;18(1):93. doi: 10.1186/s12883-018-1096-2. PMID: 29966519.

BACKGROUND: White matter hyperintensities (WMHs) are frequently detected in migraine patients. However, their significance and correlation to migraine disease burden remain unclear. This study aims to examine the correlation of WMHs with migraine features and explore the relationship between WMHs and migraine prognosis.

METHODS: A total of 69 migraineurs underwent MRI scans to evaluate WMHs. Migraine features were compared between patients with and without WMHs. After an average follow-up period of 3 years, these patients were divided into two groups, according to the reduction of headache frequency: improved and non-improved groups. The percentage and degree of WMHs were compared between these two groups.

RESULTS: A total of 24 patients (34.8%) had WMHs. Patients with WMHs were significantly older (39.0 ± 7.9 vs. 30.6 ± 10.4 years, P < 0.001) and had a longer disease duration (median: 180.0 vs. 84.0 months, P = 0.013). Furthermore, 33 patients completed the follow up period (15 patients improved and 18 patients did not improve). Patients in the non-improved group had a higher frequency of WMHs (55.6% vs. 13.3%, P = 0.027) and median WMHs score (1.0 vs. 0.0, P = 0.030).

CONCLUSIONS: WMHs can predict unfavorable migraine prognosis. Furthermore, WMHs may have a closer association with age than migraine features.

Privacy Issues in Smartphone Applications: An Analysis of Headache/Migraine Applications.

Minen MT[1], Stieglitz EJ[2], Sciortino R[3], Torous J[4].

Headache. **2018 Jul 4**. doi: 10.1111/head.13341. PMID: 29974470. [Epub ahead of print]

BACKGROUND: Headache diaries are a mainstay of migraine management. While many commercial smartphone applications (apps) have been developed for people with migraine, little is known about how well these apps protect patient information and whether they are secure to use.

OBJECTIVE: We sought to assess whether there are privacy issues surrounding apps so that physicians and patients could better understand what medical information patients are providing to the app companies, and the potential privacy implications of how the app companies (and other third parties) might use that information.

METHODS: We conducted a systematic search of the most popular "headache" and "migraine" apps and developed a database of the types of data the apps requested for input by the user and whether the apps had clear privacy policies. We also examined the content of the privacy policies.

RESULTS: Twenty-nine apps were examined (14 diary apps, 15 relaxation apps). Of the diary applications, 79% (11/14) had visible privacy policies. Of the diary apps with privacy policies, all (11/11) stated whether or not the app collects and stores information remotely.

CONCLUSIONS: Headache apps shared information with third parties, posing privacy risks partly because there are few legal protections against the sale or disclosure of data from medical apps to third parties.

HEADACHE and MIGRAINE (Continued)

Effect of Vitamin D Deficiency on the Frequency of Headaches in Migraine.

Song TJ[1], Chu MK[2], Sohn JH[3], Ahn HY[4], Lee SH[5], Cho SJ[6].

J Clin Neurol. **2018 Jul**;14(3):366-373. doi: 10.3988/jcn.2018.14.3.366. PMCID: PMC6031995. PMID: 29971976.

BACKGROUND AND PURPOSE: The risk of vitamin D deficiency varies with the season. The frequency of vitamin D deficiency in migraine patients and its association with migraine are unclear.

METHODS: We retrospectively evaluated first-visit migraine patients between January 2016 and May 2017, and investigated the demographics, season, migraine subtypes, frequency, severity, and impact of migraine, psychological and sleep variables, climate factors, and vitamin D levels. The nonfasting serum 25-hydroxyvitamin D concentration was measured to determine the vitamin D level, with deficiency of vitamin D defined as a concentration of <20 ng/mL.

RESULTS: In total, 157 patients with migraine aged 37.0±8.6 years (mean±standard deviation) were analyzed. Their serum level of vitamin D was 15.9±7.4 ng/mL. Vitamin D deficiency was present in 77.1% of the patients, and occurred more frequently in spring and winter than in summer and autumn (89.1%, 85.7%, 72.4%, and 61.7%, respectively; p=0.008). In multivariate Poisson regression analysis, monthly headache was 1.203 times (95% confidence interval=1.046-1.383, p=0.009) more frequent in patients with vitamin D deficiency than in those without deficiency after adjusting for demographics, season, migraine subtype, depression, anxiety, and sleep quality. These associations were consistently noted in subgroup analysis of episodic migraine (odds ratio=1.266, p=0.033) and chronic migraine (odds ratio=1.390, p=0.041).

CONCLUSIONS: Our study found that a larger number of monthly days with headache was related to vitamin D deficiency among migraineurs. Future studies should attempt to confirm the causal relationship between vitamin D deficiency and migraine.

CHRONIC PAIN

Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain?

Bertenthal D[1], Yaffe K[1,2,3,4], Barnes DE[1,2,3], Byers AL[1,2,3], Gibson CJ[1,5], Seal KH[1,2,5]; Chronic Effects of Neurotrauma Consortium Study Group.

Brain Inj. **2018 Jul 9**:1-9. doi: 10.1080/02699052.2018.1493535. PMID: 29985653. [Epub ahead of print]

OBJECTIVES: Opioid therapy is contraindicated in patients with traumatic brain injury (TBI) with neuropsychological impairment, yet guidelines do not consistently predict practice. We evaluated independent risk for initiation of opioid therapy among combat veterans with chronic pain diagnoses and persistent postconcussive symptoms.

METHODS: We assembled a retrospective cohort of 53 124 Iraq and Afghanistan veterans in Veterans Affairs (VA) healthcare between October 2007 and March 2015 who received chronic pain diagnoses, completed a Comprehensive TBI Evaluation (CTBIE) and had not received opioid therapy in the prior year. Primary exposure variables were self-reported severe or very severe Emotional, Vestibular, Cognitive and Somatic/Sensory symptoms measured using the Neurobehavioral Symptom Inventory. Outcome measures were initiation of short-term and long-term opioid therapy within the year following CTBIE.

RESULTS: Self-reported severe and very severe postconcussive symptoms predicted initiation of long-term and short-term opioid use for chronic pain in both unadjusted and adjusted analyses. In adjusted analyses, all four postconcussive symptom domains significantly predicted initiation of long-term opioid therapy, with Emotional symptoms being the strongest predictor [ARR = 1.68 (1.52, 1.86)].

CONCLUSIONS: Increased opioid prescribing in veterans with self-reported severe persistent postconcussive symptoms indicates a need to educate prescribers and make non-opioid pain management options available for veterans with TBI and neuropsychological sequelae.

CHRONIC PAIN (Continued)

Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study.

Campbell G[1], Hall WD[2], Peacock A[3], Lintzeris N[4], Bruno R[5], Larance B[3], Nielsen S[3], Cohen M[6], Chan G[7], Mattick RP[3], Blyth F[8], Shanahan M[3], Dobbins T[3], Farrell M[3], Degenhardt L[9].

Lancet Public Health. **2018 Jul**;3(7):e341-e350. doi: 10.1016/S2468-2667(18)30110-5. PMID: 29976328.

BACKGROUND: Interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain is increasing, because of their potential to reduce opioid dose requirements. We aimed to investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioid-sparing effects of cannabis.

METHODS: The Pain and Opioids IN Treatment study is a prospective, national, observational cohort of people with chronic non-cancer pain prescribed opioids. Participants were recruited through community pharmacies across Australia, completed baseline interviews, and were followed up with phone interviews or self-complete questionnaires yearly for 4 years. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were asked about lifetime and past year chronic pain conditions, duration of chronic non-cancer pain, pain self-efficacy, whether pain was neuropathic, lifetime and past 12-month cannabis use, number of days cannabis was used in the past month, and current depression and generalised anxiety disorder. We also estimated daily oral morphine equivalent doses of opioids. We used logistic regression to investigate cross-sectional associations with frequency of cannabis use, and lagged mixed-effects models to examine temporal associations between cannabis use and outcomes.

FINDINGS: 1514 participants completed the baseline interview and were included in the study from Aug 20, 2012, to April 14, 2014. Cannabis use was common, and by 4-year follow-up, 295 (24%) participants had used cannabis for pain. Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years). At 4-year follow-up, compared with people with no cannabis use, we found that participants who used cannabis had a greater pain severity score (risk ratio 1·14, 95% CI 1·01-1·29, for less frequent cannabis use; and 1·17, 1·03-1·32, for daily or near-daily cannabis use), greater pain interference score (1·21, 1·09-1·35; and 1·14, 1·03-1·26), lower pain self-efficacy scores (0·97, 0·96-1·00; and 0·98, 0·96-1·00), and greater generalised anxiety disorder severity scores (1·07, 1·03-1·12; and 1·10, 1·06-1·15). We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

INTERPRETATION: Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

FUNDING: National Health and Medical Research Council and the Australian Government.

CHRONIC PAIN (Continued)

Acupuncture Resolves Persistent Pain and Neuroinflammation in a Mouse Model of Chronic Overlapping Pain Conditions.

Kim S[1], Zhang X[2], O'Buckley SC[3], Cooter M[4], Park JJ[3], Nackley AG[5].

J Pain. **2018 Jul 4**. pii: S1526-5900(18)30305-5. doi: 10.1016/j.jpain.2018.05.013. PMID: 29981376. [Epub ahead of print]

Patients with chronic overlapping pain conditions have decreased levels of catechol-O-methyltransferase (COMT), an enzyme that metabolizes catecholamines. Consistent with clinical syndromes, we previously demonstrated that COMT inhibition in rodents produces persistent pain and heightened immune responses. Here, we sought to determine the efficacy of manual acupuncture in resolving persistent pain and neuroinflammation in the classic inbred C57BL/6 strain and the 'rapid healing' MRL/MpJ strain. Mice received subcutaneous osmotic minipumps to deliver the COMT inhibitor OR486 or vehicle for 13 days. On day 7 following pump implantation, acupuncture was performed at the Zusanli (ST36) point or a non-acupoint for 6 consecutive days. Behavioral responses to mechanical stimuli were measured throughout the experiment. Immunohistochemical analysis of spinal phosphorylated p38 mitogen-activated kinase (p-p38 MAPK), a marker of inflammation, and glial fibrillary acidic protein (GFAP), a marker of astrogliosis, was performed on day 13. Results demonstrated that ST36, but not sham, acupuncture resolved mechanical hypersensitivity and reduced OR486-dependent increases in p-p38 and GFAP in both strains. The magnitude of the analgesic response was greater in MRL/MpJ mice. These findings indicate acupuncture as an effective treatment for persistent pain linked to abnormalities in catecholamine signaling and, further, that analgesic efficacy may be influenced by genetic differences.

PERSPECTIVE: Chronic overlapping pain conditions (COPCs) remain ineffectively managed by conventional pharmacotherapies. Here, we demonstrate that acupuncture alleviates persistent pain and neuroinflammation linked to heightened catecholaminergic tone. Mice with superior healing capacity exhibit greater analgesic efficacy. Findings indicate acupuncture as an effective treatment for COPCs and provide insight into treatment response variability.

Chronic widespread pain prevalence in the general population: A systematic review.

Andrews P[1], Steultjens M[1], Riskowski J[1].

Eur J Pain. **2018 Jan**;22(1):5-18. doi: 10.1002/ejp.1090. PMID: 28815801. Epub 2017 Aug 17.

Chronic widespread pain (CWP) is a significant burden in communities. Understanding the impact of population-dependent (e.g., age, gender) and contextual-dependent (e.g. survey method, region, inequality level) factors have on CWP prevalence may provide a foundation for population-based strategies to address CWP. Therefore, the purpose of this study was to estimate the global prevalence of CWP and evaluate the population and contextual factors associated with CWP. A systematic review of CWP prevalence studies (1990-2017) in the general population was undertaken. Meta-analyses were conducted to determine CWP prevalence, and study population data and contextual factors were evaluated using a meta-regression. Thirty-nine manuscripts met the inclusion criteria. Study CWP prevalence ranged from 1.4% to 24.0%, with CWP prevalence in men ranging from 0.8% to 15.3% and 1.7% to 22.1% in women. Estimated overall CWP prevalence was 9.6% (8.0-11.2%). Meta-regression analyses showed gender, United Nations country development status, and human development index (HDI) influenced CWP prevalence, while survey method, region, methodological and reporting quality, and inequality showed no significant effect on the CWP estimate. Globally CWP affects one in ten individuals within the general population, with women more likely to experience CWP than men. HDI was noted to be the socioeconomic factor related to CWP prevalence, with those in more developed countries having a lower CWP prevalence than those in less developed countries. Most CWP estimates were from developed countries, and CWP estimates from countries with a lower socioeconomic position is needed to further refine the global estimate of CWP.

SIGNIFICANCE: This systematic review and meta-analysis updates the current global CWP prevalence by examining the population-level (e.g. age, gender) and contextual (e.g. country development status; survey style; reporting and methodologic quality) factors associated with CWP prevalence. This analyses provides evidence to support higher levels of CWP in countries with a lower socioeconomic position relative to countries with a higher socioeconomic position.

OTHER RESEARCH OF INTEREST

Meta-analysis of depleted uranium levels in the Middle East region.

Bešić L[1], Muhović I[2], Mrkulić F[3], Spahić L[4], Omanović A[5], Kurtovic-Kozaric A[6].

J Environ Radioact. **2018 Jun 8**;192:67-74. doi: 10.1016/j.jenvrad.2018.06.004. PMID: 29890359. [Epub ahead of print]

Since the first widespread use of depleted uranium in military in the 1991 Gulf War, the so-called "Gulf War Syndrome" has been a topic of ongoing debate. However, a low number of reliable scientific papers demonstrating the extent of possible contamination as well as its connection to the health status of residents and deployed veterans has been published. The authors of this study have therefore aimed to make a selection of data based on strict inclusion and exclusion criteria. With the goal of clarifying the extent of DU contamination after the Gulf Wars, previously published data regarding the levels of DU in the Middle East region were analyzed and presented in the form of a meta-analysis. In addition, the authors attempted to make a correlation between the DU levels and their possible effects on afflicted populations. According to results observed by comparing $^{234}U/^{238}U$ and $^{235}U/^{238}U$ isotopic activity ratios, as well as $^{235}U/^{238}U$ mass ratios in air, water, soil and food samples among the countries in the Middle East region, areas indicating contamination with DU were Al Doha, Manageesh and Um Al Kwaty in Kuwait, Al-Salman, Al-Nukhaib and Karbala in Iraq, Beirut in Lebanon and Sinai in Egypt. According to these data, no DU contamination was observed in Algeria, Israel, Afghanistan, Oman, Qatar, Iran, and Yemen. Due to the limited number of reliable data on the health status of afflicted populations, it was not possible to make a correlation between DU levels and health effects in the Middle East region.

3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial.

Mithoefer MC[1], Mithoefer AT[2], Feduccia AA[3], Jerome L[4], Wagner M[5], Wymer J[5], Holland J[6], Hamilton S[7], Yazar-Klosinski B[8], Emerson A[4], Doblin R[8].

Lancet Psychiatry. **2018 Jun**;5(6):486-497. doi: 10.1016/S2215-0366(18)30135-4. PMID: 29728331. Epub 2018 May 1.

BACKGROUND: Post-traumatic stress disorder (PTSD) is prevalent in military personnel and first responders, many of whom do not respond to currently available treatments. This study aimed to assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treating chronic PTSD in this population.

METHODS: We did a randomised, double-blind, dose-response, phase 2 trial at an outpatient psychiatric clinic in the USA. We included service personnel who were 18 years or older, with chronic PTSD duration of 6 months or more, and who had a Clinician-Administered PTSD Scale (CAPS-IV) total score of 50 or greater. Using a web-based randomisation system, we randomly assigned participants (1:1:2) to three different dose groups of MDMA plus psychotherapy: 30 mg (active control), 75 mg, or 125 mg. We masked investigators, independent outcome raters, and participants until after the primary endpoint. MDMA was administered orally in two 8-h sessions with concomitant manualised psychotherapy. The primary outcome was mean change in CAPS-IV total score from baseline to 1 month after the second experimental session. Participants in the 30 mg and 75 mg groups subsequently underwent three 100-125 mg MDMA-assisted psychotherapy sessions in an open-label crossover, and all participants were assessed 12 months after the last MDMA session. Safety was monitored through adverse events, spontaneously reported expected reactions, vital signs, and suicidal ideation and behaviour. This study is registered with ClinicalTrials.gov, number NCT01211405.

FINDINGS: Between Nov 10, 2010, and Jan 29, 2015, 26 veterans and first responders met eligibility criteria and were randomly assigned to receive 30 mg (n=7), 75 mg (n=7), or 125 mg (n=12) of MDMA plus psychotherapy. At the primary endpoint, the 75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity (mean change CAPS-IV total scores of -58·3 [SD 9·8] and -44·3 [28·7]; p=0·001) than the 30 mg group (-11·4 [12·7]). Compared with the 30 mg group, Cohen's d effect sizes were large: 2·8 (95% CI 1·19-4·39) for the 75 mg group and 1·1 (0·04-2·08) for the 125 mg group. In the open-label crossover with full-dose MDMA (100-125 mg), PTSD symptom severity significantly decreased in the group that had previously received 30 mg (p=0·01), whereas no further significant decreases were observed in the group that previously achieved a large response after 75 mg doses in the blinded segment (p=0·81). PTSD symptoms were significantly reduced at the 12-month follow-up compared with baseline after all groups had full-dose MDMA (mean CAPS-IV total score of 38·8 [SD 28·1] vs 87·1 [16·1]; p<0·0001). 85 adverse events were reported by 20 participants. Of these adverse events, four (5%) were serious: three were deemed unrelated and one possibly related to study drug treatment.

INTERPRETATION: Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in veterans and first responders.

FUNDING: Multidisciplinary Association for Psychedelic Studies.

OTHER RESEARCH OF INTEREST (Continued)

Big Data and Predictive Analytics: Recalibrating Expectations.

Shah ND[1], Steyerberg EW[2], Kent DM[3].

JAMA. **2018 May 29**. doi: 10.1001/jama.2018.5602. PMID: 29813156. [Epub ahead of print]

With the routine use of electronic health records (EHRs) in hospitals, health systems, and physician practices, there has been rapid growth in the availability of health care data over the last decade. In addition to the structured data in EHRs, new methods such as natural language processing can derive meaning from unstructured data, permitting the capture of substantial clinical information embedded in clinical notes. Furthermore, the growth in the availability of registries and claims data and the linkages between all these data sources have created a big data platform in health care, vast in both size and scope.

Concurrently, new computational machine learning approaches promise ever-more-accurate prediction. The marvel of Google and of Watson, the inexorability of Moore's law (ie, computing power doubles every 2 years for the same cost), suggest a future in which medicine will be transformed into an information science, and each clinical decision may be optimized based on a forecasting of outcomes under alternative treatment options, beyond the knowledge and understanding of the individual physician.

Yet despite these innovations and those to come, quantitative risk prediction in medicine has been available for several decades, based on more classical statistical learning from more structured data sources. Despite reports that risk models outperform physicians in prognostic accuracy, application in actual clinical practice remains limited. For example, more than 1000 cardiovascular clinical prediction models have been developed and cataloged, yet only a small number of these are routinely used to support decision making in clinical care. It seems unlikely that incremental improvements in discriminative performance of the kind typically demonstrated in machine learning research will ultimately drive a major shift in clinical care. In this Viewpoint, we describe 4 major barriers to useful risk prediction that may not be easily overcome by new methods in machine learning and, in some instances, may be more difficult to overcome in the era of big data.

[Link to full-text continuation of article in JAMA Viewpoint.]

Insomnia Symptoms Among Female Veterans: Prevalence, Risk Factors, and the Impact on Psychosocial Functioning and Health Care Utilization.

Babson KA[1], Wong AC[2], Morabito D[1], Kimerling R[1,2].

J Clin Sleep Med. **2018 Jun 15**;14(6):931-939. doi: 10.5664/jcsm.7154. PMCID: PMC5991965. PMID: 29852900.

STUDY OBJECTIVES: To examine the prevalence of self-reported insomnia symptoms, identify subgroups of female veterans with clinically significant insomnia symptoms, and examine the effect on psychosocial functioning and health care utilization.

METHODS: Cross-sectional analysis of insomnia symptoms and associated characteristics among a stratified random sample of female veterans using Department of Veterans Affairs primary care facilities between October 1, 2010 and September 30, 2011 (n = 6,261) throughout the United States. The primary outcome was reported presence of insomnia symptoms. Other variables included psychological disorders, chronic conditions, chronic pain, and demographic variables.

RESULTS: Overall, 47.39% of female veterans screened positively for insomnia symptoms. They differed demographically from those without insomnia symptoms and reported more substance use, chronic physical conditions, and psychological conditions. Receiver operating characteristic analysis indicated the primary factor that differentiated those with versus those without insomnia symptoms was depression. Individuals were further differentiated based on presence of pain and posttraumatic stress disorder. Results yielded eight homogenous subgroups of women at low and high risk of experiencing insomnia symptoms.

CONCLUSIONS: Sleep problems are common among female veterans (47.39%) despite limited diagnosis of sleep disorders (0.90%). Eight unique subgroups of female veterans with both low and high insomnia symptoms were observed. These subgroups differed in terms of psychosocial functioning and health care utilization, with those with depression, posttraumatic stress disorder, and pain having the poorest outcomes. These results shed light on the prevalence of insomnia symptoms experienced among female veterans and the effect on psychosocial functioning and health care utilization. Results can inform targeted detection and customized treatment among female veterans.

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