GULF WAR ILLNESS

Neurotoxicity in acute and repeated organophosphate exposure.

Naughton SX[1], Terry AV Jr[2].

Toxicology. **2018 Aug 22**. pii: S0300-483X(18)30264-6. doi: 10.1016/j.tox.2018.08.011. PMID: 30144465. [Epub ahead of print]

The term organophosphate (OP) refers to a diverse group of chemicals that are found in hundreds of products worldwide. As pesticides, their most common use, OPs are clearly beneficial for agricultural productivity and the control of deadly vector-borne illnesses. However, as a consequence of their widespread use, OPs are now among the most common synthetic chemicals detected in the environment as well as in animal and human tissues. This is an increasing environmental concern because many OPs are highly toxic and both accidental and intentional exposures to OPs resulting in deleterious health effects have been documented for decades. Some of these deleterious health effects include a variety of long-term neurological and psychiatric disturbances including impairments in attention, memory, and other domains of cognition. Moreover, some chronic illnesses that manifest these symptoms such as Gulf War Illness and Aerotoxic Syndrome have (at least in part) been attributed to OP exposure. In addition to acute acetylcholinesterase inhibition, OPs may affect a number of additional targets that lead to oxidative stress, axonal transport deficits, neuroinflammation, and autoimmunity. Some of these targets could be exploited for therapeutic purposes. The purpose of this review is thus to: 1) describe the important uses of organophosphate (OP)-based compounds worldwide, 2) provide an overview of the various risks and toxicology associated with OP exposure, particularly long-term neurologic and psychiatric symptoms, 3) discuss mechanisms of OP toxicity beyond cholinesterase inhibition, 4) review potential therapeutic strategies to reverse the acute toxicity and long term deleterious effects of OPs.

CHRONIC FATIGUE SYNDROME

Loss of Transient Receptor Potential Melastatin 3 ion channel function in natural killer cells from Chronic Fatigue Syndrome/Myalgic Encephalomyelitis patients.

Cabanas H[1,2], Muraki K[3], Eaton N[4,5], Balinas C[4,5], Staines D[4,5], Marshall-Gradisnik S[4,5].

Mol Med. **2018 Aug 14**;24(1):44. doi: 10.1186/s10020-018-0046-1. PMID: 30134818.

BACKGROUND: Chronic Fatigue Syndrome (CFS)/ Myalgic Encephalomyelitis (ME) is a debilitating disorder that is accompanied by reduced cytotoxic activity in natural killer (NK) cells. NK cells are an essential innate immune cell, responsible for recognising and inducing apoptosis of tumour and virus infected cells. Calcium is an essential component in mediating this cellular function. Transient Receptor Potential Melastatin 3 (TRPM3) cation channels have an important regulatory role in mediating calcium influx to help maintain cellular homeostasis. Several single nucleotide polymorphisms have been reported in TRPM3 genes from isolated peripheral blood mononuclear cells, NK and B cells in patients with CFS/ME and have been proposed to correlate with illness presentation. Moreover, a significant reduction in both TRPM3 surface expression and intracellular calcium mobilisation in NK cells has been found in CFS/ME patients compared with healthy controls. Despite the functional importance of TRPM3, little is known about the ion channel function in NK cells and the epiphenomenon of CFS/ME. The objective of the present study was to characterise the TRPM3 ion channel function in NK cells from CFS/ME patients in comparison with healthy controls using whole cell patch-clamp techniques.

METHODS: NK cells were isolated from 12 age- and sex-matched healthy controls and CFS patients. Whole cell electrophysiology recording has been used to assess TRPM3 ion channel activity after modulation with pregnenolone sulfate and ononetin.

RESULTS: We report a significant reduction in amplitude of TRPM3 current after pregnenolone sulfate stimulation in isolated NK cells from CFS/ME patients compared with healthy controls. In addition, we found pregnenolone sulfate-evoked ionic currents through TRPM3 channels were significantly modulated by ononetin in isolated NK cells from healthy controls compared with CFS/ME patients.

CONCLUSIONS: TRPM3 activity is impaired in CFS/ME patients suggesting changes in intracellular Ca^{2+} concentration, which may impact NK cellular functions. This investigation further helps to understand the intracellular-mediated roles in NK cells and confirm the potential role

HEADACHE and MIGRAINE

Correlation of neurochemical and imaging markers in migraine: PACAP38 and DTI measures.

Veréb D[1], Szabó N[1], Tuka B[1], Tajti J[1], Király A[1], Faragó P[1], Kocsis K[1], Tóth E[1], Kincses B[1], Bagoly T[1], Helyes Z[1], Vécsei L[1], Kincses ZT[2].

Neurology. **2018 Aug 22**. pii: 10.1212/WNL.0000000000006201. doi: 10.1212/WNL.0000000000006201. PMID: 30135251. [Epub ahead of print]

OBJECTIVE: To examine whether interictal plasma pituitary adenylate cyclase-activating peptide 38-like immunoreactivity (PACAP38-LI) shows correlation with the microstructural integrity of the white matter in migraine.

METHODS: Interictal plasma PACAP38-LI was measured by radioimmunoassay in 26 patients with migraine (24 women) who underwent diffusion tensor imaging afterward using a 1.5-tesla magnetic resonance scanner. Data were analyzed using tract-based spatial statistics included in FMRIB's Software Library.

RESULTS: Interictal plasma PACAP38-LI showed significant correlation with mean diffusivity ($p < 0.0179$) mostly in the bilateral occipital white matter spreading into parietal and temporal white matter. Axial and radial diffusivity showed positive correlation with interictal PACAP38-LI ($p < 0.0432$ and $p < 0.0418$, respectively) in the left optic radiation and left posterior corpus callosum. Fractional anisotropy did not correlate significantly with PACAP38-LI. With disease duration as a nuisance regressor in the model, PACAP38-LI correlated with axial and mean diffusivity in the left thalamus ($p < 0.01$).

CONCLUSION: We report a link between PACAP38, a pathobiologically important neurochemical biomarker, and imaging markers of the disease that may bolster further research into the role of PACAP38 in migraine.

Unnecessary Neuroimaging for Patients With Primary Headaches.

Wang R[1], Liu R[1], Dong Z[1], Su H[1], Ao R[1], Liu Y[1], Wang Y[2], Ma L[2], Yu S[1].

Headache. **2018 Aug 23**. doi: 10.1111/head.13397. PMID: 30136725. [Epub ahead of print]

Background - Headache may be due to either a primary or secondary disorder, and neuroimaging assessments can play an important role when differentiating between these types of headache. Although many studies have reported no significant differences between primary headache patients and the general population in terms of abnormal neuroimaging findings, others have shown that neuroimaging may be employed to rule out secondary causes of headache that could impact morbidity and mortality. This issue remains under debate. Thus, the present study compared the neuroimaging findings of headache patients and healthy controls.

Methods - This study recruited 1070 healthy controls and 1070 primary headache patients from the Chinese People's Liberation Army General Hospital. The primary headache patients were diagnosed by computerized clinical decision support systems, and re-diagnosed by a specialist. All participants were assessed with either computed tomography or magnetic resonance imaging (MRI) scans. The neuroimaging findings were classified as significant abnormalities, non-significant abnormalities, or normal.

Results - All the significant abnormalities were found using MRI scans. Significant abnormalities were identified in 4 primary headache patients (0.58%) and 5 healthy controls (0.73%); the rate of significant abnormalities was not significant different between both groups (P > .05).

Conclusions - The present study found that neuroimaging was unnecessary for the primary headache patients.

HEADACHE and MIGRAINE (Continued)

Induction of migraine-like headache, but not aura, by cilostazol in patients with migraine with aura.

Butt JH[1], Rostrup E[2], Hansen AS[1], Lambertsen KL[3,4,5], Kruuse C[1].

Brain. **2018 Aug 22**. doi: 10.1093/brain/awy228. PMID: 30137217. [Epub ahead of print]

Whether migraine headache and migraine aura share common pathophysiological mechanisms remains to be understood. Cilostazol causes cAMP accumulation and provokes migraine-like headache in migraine patients without aura. We investigated if cilostazol induces aura and migraine-like headache in patients with migraine with aura and alters peripheral endothelial function and levels of endothelial markers. In a randomized, double-blinded, placebo-controlled crossover study, 16 patients with migraine with aura (of whom 12 patients exclusively had attacks of migraine with aura) received 200 mg cilostazol (Pletal®) or placebo on two separate days. The development, duration, and characteristics of aura and headache were recorded using a questionnaire. Peripheral endothelial function was assessed by digital pulse amplitude tonometry using EndoPAT2000, and endothelial markers (VCAM1, E-selectin, and VEGFA) were measured. After administration of cilostazol, 14 patients (88%) experienced headache compared with six patients (38%) after placebo (P = 0.009). The headache in 12 patients (75%) after cilostazol and one patient (6%) after placebo fulfilled the criteria for migraine-like attacks (P = 0.0002). Patients reported that the attack mimicked the headache phase during their usual migraine attacks. However, aura symptoms were elicited in one patient after cilostazol and one patient after placebo. Further, endothelial function, as assessed by peripheral arterial tonometry, and endothelial markers were not significantly altered by cilostazol. Accumulation of cAMP by cilostazol induces migraine-like headache, but not aura, in patients with migraine with aura, even in those who exclusively reported attacks of migraine with aura in their spontaneous attacks. These findings further support dissociation between the aura and the headache phase with a yet unknown trigger for the aura and link between aura and headache. In addition, cilostazol administration did not significantly alter endothelial function, as assessed by peripheral arterial tonometry, or the endothelial markers, VCAM1, E-selectin, and VEGFA. However, post hoc analyses showed that our study was statistically underpowered for these outcomes.

Treatment of acute migraine by a partial rebreathing device: A randomized controlled pilot study.

Fuglsang CH[1], Johansen T[2,3], Kaila K[4], Kasch H[5], Bach FW[1].

Cephalalgia. **2018 Aug 22**:333102418797285. doi: 10.1177/0333102418797285. PMID: 30134739. [Epub ahead of print]

Background: Impaired brain oxygen delivery can trigger and exacerbate migraine attacks. Normoxic hypercapnia increases brain oxygen delivery markedly by vasodilation of the cerebral vasculature, and hypercapnia has been shown to abort migraine attacks. Stable normoxic hypercapnia can be induced by a compact partial rebreathing device. This pilot study aimed to provide initial data on the device's efficacy and safety.

Methods: Using a double-blinded, randomized, cross-over study design, adult migraine-with-aura patients self-administered the partial rebreathing device or a sham device for 20 minutes at the onset of aura symptoms.

Results: Eleven participants (mean age 35.5, three men) self-treated 41 migraine attacks (20 with the partial rebreathing device, 21 with sham). The partial rebreathing device increased mean End Tidal CO_2 by 24%, while retaining mean oxygen saturation above 97%. The primary end point (headache intensity difference between first aura symptoms and two hours after treatment (0-3 scale) - active/sham difference) did not reach statistical significance (-0.55 (95% CI: -1.13-0.04), p = 0.096), whereas the difference in percentage of attacks with pain relief at two hours was significant (p = 0.043), as was user satisfaction (p = 0.022). A marked efficacy increase was seen from first to second time use of the partial rebreathing device. No adverse events occurred, and side effects were absent or mild.

Conclusion: Normoxic hypercapnia shows promise as an adjunctive/alternative migraine treatment, meriting further investigation in a larger population. Clinical study registered at ClinicalTrials.gov with identifier NCT03472417.

CHRONIC PAIN

Increased Nonopioid Chronic Pain Treatment in the Veterans Health Administration, 2010-2016.

Frank JW[1,2], Carey E[1], Nolan C[1], Kerns RD[3,4], Sandbrink F[5,6], Gallagher R[7,8], Ho PM[1,2].

Pain Med. **2018 Aug 21**. doi: 10.1093/pm/pny149. [Epub ahead of print]

RAC ADMIN SUMMARY REVIEW of non-abstracted copyright-protected article: Chronic pain that disproportionately impacts veterans remains an important challenge for the Veterans Health Administration (VHA) which implemented multiple system-level programs to support guideline-concordant chronic pain care in pain-related treatment utilization from 2010 to 2016. Among veterans who have increased incidence of chronic pain, seven of nine nonopioid treatment modalities are utilized with an increased proportion of veterans utilizing multiple modalities. Future emphasis in VHA includes patient-centered integration of these modalities and assessment of the impact of multimodal care on patient outcomes.

In the VHA, the stepped care model for pain management guides delivery of multimodal chronic pain care with population-based screening, assessment, and management of chronic pain. In collaboration with the primary care team, the full range of low-intensity interventions is delivered in primary care settings with timely access to pain specialty teams that provide more intensive treatments targeted to individuals with more complex chronic pain.

Since 2003, guidelines from the Departments of Veterans Affairs and Defense have emphasized nonopioid treatments for firstline treatment of chronic pain. In recent years, opioid medication prescribing has been under increasing scrutiny given inadequate evidence of long-term benefit and growing evidence of harms. In 2013, the VHA implemented its Opioid Safety Initiative, a system-wide program to improve the safety of opioid prescribing, which has reduced high-risk medication prescribing.

This article reviews recent changes in utilization of nonopioid chronic pain treatment modalities and use of a published algorithm and electronic health record data to identify and describe the cohort of veterans receiving primary care for chronic pain between 2010, and 2015.

[View article full text and references online in Pain Medicine at the Oxford Academic website.]

The association between areas of secondary hyperalgesia and volumes of the caudate nuclei and other pain relevant brain structures-A 3-tesla MRI study of healthy men.

Hansen MS[1,2], Asghar MS[1], Wetterslev J[3], Pipper CB[4], Mårtensson J[5], Becerra L[6], Christensen A[2], Nybing JD[2], Havsteen I[2], Boesen M[7], Dahl JB[8].

PLoS One. **2018 Aug 21**;13(8):e0201642. doi: 10.1371/journal.pone.0201642. PMID: 30130373. eCollection 2018.

INTRODUCTION: Central sensitization plays a pivotal role in maintenance of pain and is believed to be intricately involved in several chronic pain conditions. One clinical manifestation of central sensitization is secondary hyperalgesia. The degree of secondary hyperalgesia presumably reflects individual levels of central sensitization. The objective of this study was to investigate the association between areas of secondary hyperalgesia and volumes of the caudate nuclei and other brain structures involved in pain processing.

MATERIALS AND METHODS: We recruited 121 healthy male participants; 118 were included in the final analysis. All participants underwent whole brain magnetic resonance imaging (MRI). Prior to MRI, all participants underwent pain testing. Secondary hyperalgesia was induced by brief thermal sensitization. Additionally, we recorded heat pain detection thresholds (HPDT), pain during one minute thermal stimulation (p-TS) and results of the Pain Catastrophizing Scale (PCS) and Hospital Anxiety and Depression score (HADS).

RESULTS: We found no significant associations between the size of the area of secondary hyperalgesia and the volume of the caudate nuclei or of the following structures: primary somatosensory cortex, anterior and mid cingulate cortex, putamen, nucleus accumbens, globus pallidus, insula and the cerebellum. Likewise, we found no significant associations between the volume of the caudate nuclei and HPDTs, p-TS, PCS and HADS.

CONCLUSIONS: Our findings indicate that the size of the secondary hyperalgesia area is not associated with the volume of brain structures relevant for pain processing, suggesting that the propensity to develop central sensitization, assessed as secondary hyperalgesia, is not correlated to brain structure volume.

CHRONIC PAIN (Continued)

Quality Indicators to Assess Quality of Pain Clinic Care From Perspective of Patients with Chronic Pain: Development, Usability, Comprehensibility, and Psychometric Quality of the QiPPP Questionnaire.

de Meij N[1], Köke A[2,3,4], IlonaThomassen[5], Kallewaard JW[6], van Kleef M[1], van der Weijden T[7].

Pain. **2018 Aug 14**. doi: 10.1097/j.pain.0000000000001371. PMID: 30130300. [Epub ahead of print]

To address the lack of appropriate patient-defined quality indicators (QIs) for assessment of pain clinic care in the Netherlands, we developed the "Quality Indicators - Pain Patients' Perspective" (QiPPP) questionnaire. QIs are widely used to measure the quality of the structure, process, and outcome of health care. The Pain Patient United Consortium, together with the University Pain Centre of Maastricht, developed QIs for assessment of care. The aim of this study was to develop QIs from the perspective of patients with chronic pain for assessment of the care provided by a pain clinic, and to validate them on usability, comprehensibility, and psychometric quality in daily pain practice. Quality as defined by patients with chronic pain (in survey and focus groups) was prioritized by consensus and transformed into QI. A first set was tested and fine-tuned resulting in the QiPPP questionnaire. Five participating pain clinics distributed 200 questionnaires among consecutive patients with chronic pain under treatment. To examine the dimensionality of the QIs, patient responses were analyzed on the basis of reporting frequencies and findings of principal component analysis. For construct validation, the influence of patient characteristics was observed in three components. A total of 547 (54.7%) populated QiPPP questionnaires (response rate, 58.9%) were analyzed. The mean score for patient comprehensibility was 8.6 ± 1.4. The final QiPPP questionnaire included 21 QIs (18 process; 3 outcome) distributed over 7 domains. The QiPPP questionnaire was of sufficient psychometric quality and found to be useful and understandable by patients with chronic pain.

Analgesic Effects Evoked by Real and Imagined Acupuncture: A Neuroimaging Study.

Cao J[1,2], Tu Y[1], Orr SP[1], Lang C[1], Park J[1], Vangel M[3], Chen L[4], Gollub R[1,5], Kong J[1,5].

Cereb Cortex. **2018 Aug 23**. doi: 10.1093/cercor/bhy190. PMID: 30137262. [Epub ahead of print]

Acupuncture can provide therapeutic analgesic benefits but is limited by its cost and scheduling difficulties. Guided imagery is a commonly used method for treating many disorders, such as chronic pain. The present study examined a novel intervention for pain relief that integrates acupuncture with imagery called video-guided acupuncture imagery treatment (VGAIT). A total of 27 healthy subjects were recruited for a crossover-design study that included 5 sessions administered in a randomized order (i.e., baseline and 4 different interventions). We investigated changes in pain threshold and fMRI signals modulated by: 1) VGAIT, watching a video of acupuncture previously administered on the participant's own body at baseline while imagining it being concurrently applied; 2) a VGAIT control condition, watching a video of a cotton swab touching the skin; 3) real acupuncture; and 4) sham acupuncture. Results demonstrated that real acupuncture and VGAIT significantly increased pain threshold compared with respective control groups. Imaging showed that real acupuncture produced greater activation of the insula compared with VGAIT. VGAIT produced greater deactivation at the rostral anterior cingulate cortex. Our findings demonstrate that VGAIT holds potential clinical value for pain management.

OTHER RESEARCH OF INTEREST

Expanding Veterans' Access to Cancer Clinical Trials

Rita Rubin, MA

JAMA. Health Agencies Update. **2018 Aug 28**;320(8):748. doi:10.1001/jama.2018.12069.

The National Cancer Institute (NCI) and the Department of Veterans Affairs (VA) are collaborating to make clinical trials of novel cancer treatments more accessible to veterans.

Although the VA already conducts clinical trials in cancer and other diseases at more than 100 sites nationwide, its facilities often have challenges initiating and completing trials, in part because their staffs might lack adequate support to handle regulatory and administrative tasks involved in these studies, according to the agency.

Through the NCI and VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE), the NCI will provide infrastructure funding to 12 VA facilities across the country to enable their participation in NCI-sponsored clinical trials. In turn, the VA will establish a network within its national health care system to focus on NCI trial goals.

The agencies' collaboration will continue for up to 2 years, during which time the 12 VA facilities in NAVIGATE are expected to establish the capability to continue participating in NCI trials after the program ends. The NAVIGATE sites will also establish best practices and share insights to help other VA facilities initiate new studies and enroll more veterans in cancer clinical trials.

The NAVIGATE VA facilities are in Atlanta; Charleston, South Carolina; Denver; Durham, North Carolina; Hines, Illinois; Long Beach, California; Minneapolis; New York City; Palo Alto, California; Portland, Oregon; San Antonio; and West Haven, Connecticut.

"This agreement will not only provide veterans greater access to NCI clinical trials, it will enhance accrual [to trials]," James Doroshow, MD, NCI deputy director for clinical and translational research, said in a statement.

Overdose Risk Associated with Opioid Use upon Hospital Discharge in Veterans Health Administration Surgical Patients.

Mudumbai SC[1,2,3], Lewis ET[2,4], Oliva EM[2,4], Chung PD[1], Harris B[2], Trafton J[2,4], Mariano ER[1,3], Wagner T[2,5,6], Clark JD[1,3], Stafford RS[7].

Pain Med. **2018 Aug 21**. doi: 10.1093/pm/pny150. PMID: 30137452. [Epub ahead of print]

Objective: To determine an association between opioid use upon hospital discharge (ongoing and newly started) in surgical patients and risks of opioid overdose and delirium for the first year.

Design: Retrospective, cohort study.

Setting: Population-level study of Veterans Health Administration patients.

Subjects: All Veterans Health Administration patients (N = 64,391) who underwent surgery in 2011, discharged after one or more days, and without a diagnosis of opioid overdose or delirium from 90 days before admission through 30 days postdischarge (to account for additional opioid dosing in the context of chronic use).

Methods: Patients' opioid use was categorized as 1) no opioids, 2) tramadol only, 3) short-acting only, 4) long-acting only, 5) short- and long-acting. We calculated unadjusted incidence rates and the incidence rate ratio (IRR) for opioid overdose and drug delirium for two time intervals: postdischarge days 0-30 and days 31-365. We then modeled outcomes of opioid overdose and delirium for postdischarge days 31-365 using a multivariable extended Cox regression model. Sensitivity analysis examined risk factors for overdose for postdischarge days 0-30.

Results: Incidence of overdose was 11-fold greater from postdischarge days 0-30 than days 31-365: 26.3 events/person-year (N = 68) vs 2.4 events/person-year (N = 476; IRR = 10.80, 95% confidence interval [CI] = 8.37-13.92). Higher-intensity opioid use was associated with increasing risk of overdose for the year after surgery, with the highest risk for the short- and long-acting group (hazard ratio = 4.84, 95% CI = 3.28-7.14). Delirium (IRR = 10.66, 95% CI = 7.96-14.29) was also associated with higher opioid intensity.

Conclusions: Surgical patients should be treated with the lowest effective intensity of opioids and be monitored to prevent opioid-related adverse events.

OTHER RESEARCH OF INTEREST (Continued)

Opioid prescribing decreases after learning of a patient's fatal overdose.

Doctor JN[1], Nguyen A[2], Lev R[3], Lucas J[4], Knight T[2], Zhao H[2], Menchine M[5].

Science. **2018 Aug 10**;361(6402):588-590. doi: 10.1126/science.aat4595. PMID: 30093595.

Most opioid prescription deaths occur among people with common conditions for which prescribing risks outweigh benefits. General psychological insights offer an explanation: People may judge risk to be low without available personal experiences, may be less careful than expected when not observed, and may falter without an injunction from authority. To test these hypotheses, we conducted a randomized trial of 861 clinicians prescribing to 170 persons who subsequently suffered fatal overdoses. Clinicians in the intervention group received notification of their patients' deaths and a safe prescribing injunction from their county's medical examiner, whereas physicians in the control group did not. Milligram morphine equivalents in prescriptions filled by patients of letter recipients versus controls decreased by 9.7% (95% confidence interval: 6.2 to 13.2%; $P < 0.001$) over 3 months after intervention. We also observed both fewer opioid initiates and fewer high-dose opioid prescriptions by letter recipients.

Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study.

Larochelle MR[1], Bernson D[2], Land T[2], Stopka TJ[3], Wang N[4], Xuan Z[5], Bagley SM[1], Liebschutz JM[6], Walley AY[7].

Ann Intern Med. **2018 Aug 7**;169(3):137-145. doi: 10.7326/M17-3107. Epub 2018 Jun 19.

Background: Opioid overdose survivors have an increased risk for death. Whether use of medications for opioid use disorder (MOUD) after overdose is associated with mortality is not known.

Objective: To identify MOUD use after opioid overdose and its association with all-cause and opioid-related mortality.

Design: Retrospective cohort study.

Setting: 7 individually linked data sets from Massachusetts government agencies.

Participants: 17 568 Massachusetts adults without cancer who survived an opioid overdose between 2012 and 2014.

Measurements: Three types of MOUD were examined: methadone maintenance treatment (MMT), buprenorphine, and naltrexone. Exposure to MOUD was identified at monthly intervals, and persons were considered exposed through the month after last receipt. A multivariable Cox proportional hazards model was used to examine MOUD as a monthly time-varying exposure variable to predict time to all-cause and opioid-related mortality.

Results: In the 12 months after a nonfatal overdose, 2040 persons (11%) enrolled in MMT for a median of 5 months (interquartile range, 2 to 9 months), 3022 persons (17%) received buprenorphine for a median of 4 months (interquartile range, 2 to 8 months), and 1099 persons (6%) received naltrexone for a median of 1 month (interquartile range, 1 to 2 months). Among the entire cohort, all-cause mortality was 4.7 deaths (95% CI, 4.4 to 5.0 deaths) per 100 person-years and opioid-related mortality was 2.1 deaths (CI, 1.9 to 2.4 deaths) per 100 person-years. Compared with no MOUD, MMT was associated with decreased all-cause mortality (adjusted hazard ratio [AHR], 0.47 [CI, 0.32 to 0.71]) and opioid-related mortality (AHR, 0.41 [CI, 0.24 to 0.70]). Buprenorphine was associated with decreased all-cause mortality (AHR, 0.63 [CI, 0.46 to 0.87]) and opioid-related mortality (AHR, 0.62 [CI, 0.41 to 0.92]). No associations between naltrexone and all-cause mortality (AHR, 1.44 [CI, 0.84 to 2.46]) or opioid-related mortality (AHR, 1.42 [CI, 0.73 to 2.79]) were identified.

Limitation: Few events among naltrexone recipients preclude confident conclusions.

Conclusion: A minority of opioid overdose survivors received MOUD. Buprenorphine and MMT were associated with reduced all-cause and opioid-related mortality.

Primary Funding Source: National Center for Advancing Translational Sciences of the National Institutes of Health.

OTHER RESEARCH OF INTEREST (Continued)

Co-regulatory networks of human serum proteins link genetics to disease.

Emilsson V[#1,2], Ilkov M[#3], Lamb JR[#4], Finkel N[5], Gudmundsson EF[3], Pitts R[5], Hoover H[5], Gudmundsdottir V[3], Horman SR[6], Aspelund T[3,7], Shu L[8], Trifonov V[6], Sigurdsson S[3], Manolescu A[9], Zhu J[10], Olafsson Ö[3], Jakobsdottir J[3], Lesley SA[6], To J[6], Zhang J[6], Harris TB[11], Launer LJ[11], Zhang B[10], Eiriksdottir G[3], Yang X[8], Orth AP[6], Jennings LL[#5], Gudnason V[#1,12].

Science. **2018 Aug 24**;361(6404):769-773. doi: 10.1126/science.aaq1327. PMID: 30072576. Epub 2018 Aug 2.

Proteins circulating in the blood are critical for age-related disease processes; however, the serum proteome has remained largely unexplored. To this end, 4137 proteins covering most predicted extracellular proteins were measured in the serum of 5457 Icelanders over 65 years of age. Pairwise correlation between proteins as they varied across individuals revealed 27 different network modules of serum proteins, many of which were associated with cardiovascular and metabolic disease states, as well as overall survival. The protein modules were controlled by cis- and trans-acting genetic variants, which in many cases were also associated with complex disease. This revealed co-regulated groups of circulating proteins that incorporated regulatory control between tissues and demonstrated close relationships to past, current, and future disease states.

Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.

GBD 2016 Alcohol Collaborators.

Lancet. **2018 Aug 23**. pii: S0140-6736(18)31310-2. doi: 10.1016/S0140-6736(18)31310-2. PMID: 30146330. [Epub ahead of print]

BACKGROUND: Alcohol use is a leading risk factor for death and disability, but its overall association with health remains complex given the possible protective effects of moderate alcohol consumption on some conditions. With our comprehensive approach to health accounting within the Global Burden of Diseases, Injuries, and Risk Factors Study 2016, we generated improved estimates of alcohol use and alcohol-attributable deaths and disability-adjusted life-years (DALYs) for 195 locations from 1990 to 2016, for both sexes and for 5-year age groups between the ages of 15 years and 95 years and older.

METHODS: Using 694 data sources of individual and population-level alcohol consumption, along with 592 prospective and retrospective studies on the risk of alcohol use, we produced estimates of the prevalence of current drinking, abstention, the distribution of alcohol consumption among current drinkers in standard drinks daily (defined as 10 g of pure ethyl alcohol), and alcohol-attributable deaths and DALYs. We made several methodological improvements compared with previous estimates: first, we adjusted alcohol sales estimates to take into account tourist and unrecorded consumption; second, we did a new meta-analysis of relative risks for 23 health outcomes associated with alcohol use; and third, we developed a new method to quantify the level of alcohol consumption that minimises the overall risk to individual health.

FINDINGS: Globally, alcohol use was the seventh leading risk factor for both deaths and DALYs in 2016, accounting for 2·2% (95% uncertainty interval [UI] 1·5-3·0) of age-standardised female deaths and 6·8% (5·8-8·0) of age-standardised male deaths. Among the population aged 15-49 years, alcohol use was the leading risk factor globally in 2016, with 3·8% (95% UI 3·2-4·3) of female deaths and 12·2% (10·8-13·6) of male deaths attributable to alcohol use. For the population aged 15-49 years, female attributable DALYs were 2·3% (95% UI 2·0-2·6) and male attributable DALYs were 8·9% (7·8-9·9). The three leading causes of attributable deaths in this age group were tuberculosis (1·4% [95% UI 1·0-1·7] of total deaths), road injuries (1·2% [0·7-1·9]), and self-harm (1·1% [0·6-1·5]). For populations aged 50 years and older, cancers accounted for a large proportion of total alcohol-attributable deaths in 2016, constituting 27·1% (95% UI 21·2-33·3) of total alcohol-attributable female deaths and 18·9% (15·3-22·6) of male deaths. The level of alcohol consumption that minimised harm across health outcomes was zero (95% UI 0·0-0·8) standard drinks per week.

INTERPRETATION: Alcohol use is a leading risk factor for global disease burden and causes substantial health loss. We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption, and the level of consumption that minimises health loss is zero. These results suggest that alcohol control policies might need to be revised worldwide, refocusing on efforts to lower overall population-level consumption.

FUNDING: Bill & Melinda Gates Foundation.

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