GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

No Updates this Week for Chronic Fatigue Syndrome.

HEADACHE and MIGRAINE

Problematic presentation and use of efficacy measures in current trials of CGRP monoclonal antibodies for episodic migraine prevention: A mini-review.

Tfelt-Hansen P[1], Diener HC[2], Steiner TJ[3,4].

Cephalalgia. **2019 Sep 23**:333102419877663. doi: 10.1177/0333102419877663. PMID: 31547694. [Epub ahead of print]

BACKGROUND: In trials of monoclonal antibodies against calcitonin gene-related peptide or its receptor for prevention of episodic migraine, we observed two problematic aspects: a) The graphic presentations; b) the methods of calculating "response rates" (≥50% decrease of monthly migraine days from baseline).

OBSERVATIONS: Decrease in monthly migraine days is presented, over time, in figures on a downward (negative) scale from zero at baseline, with the ordinate stopped just beyond the maximum effect of the active drugs. In one trial, decreases in monthly migraine days were -1.8 after placebo, -3.2 after erenumab 70 mg and -3.7 after erenumab 140 mg, with the ordinate stopped at -4.5. The reader can perceive only a relative 2-fold benefit of erenumab versus placebo. If, however, treatment periods are compared with baseline in bar charts, MMDs persisting after treatment in the same trial can be illustrated as follows, creating a different perception: 78% for placebo, 61% for erenumab 70 mg, and 55% for erenumab 140 mg. In the nine trials, "response rates" defined as above were calculated in five different ways, taking different numbers of treatment months into account in comparisons with the one-month baseline. This makes comparisons impossible.

SUGGESTIONS FOR IMPROVEMENTS: Mean monthly migraine days before and after treatment should be presented in a bar chart. Such figures, presenting persisting MMDs, are more clinically relevant and less misleading than decreases from baseline. The definition and methods of calculating and presenting "50% response rates" should be standardized by the Drug Trial Committee of the International Headache Society.

CHRONIC PAIN

Motor cortex function in fibromyalgia: a pilot study involving near-infrared spectroscopy and co-recording of laser-evoked potentials.

Gentile E, Ricci K, Delussi M, de Tommaso M.

Funct Neurol. **2019 Apr/Jun**;34(2):107-118. PMID: 31556391.

Interaction between the motor and nociceptive systems seems to play an important role in chronic pain. In this pilot study we used a combination of functional near-infrared spectroscopy (FNIRS) and laserevoked potentials (LEPs) during concurrent finger tapping task and noxious laser stimulation in fibromyalgia (FM) patients and controls. The study included 9 healthy subjects and 15 FM patients. During concurrent FNIRS and LEP recording, participants were required either to remain in resting relaxed condition or to execute a finger tapping task with the right hand. In the control group, the left motor cortex showed increased oxyhaemoglobin levels, while the early N1 LEP component was reduced, during the finger tapping task. In FM patients, motor cortex oxyhaemoglobin concentrations were lower during movement, which did not reduce LEPs. The left motor cortex oxyhaemoglobin concentrations had 79.2% diagnostic accuracy. The interplay between motor and pain-related circuits seems to be dysfunctional in FM patients. These results may support a role for motor cortex modulation in the treatment of this disabling disease.

CHRONIC PAIN (Continued)

The association between vitamin D concentration and pain: a systematic review and meta-analysis.

Wu Z[1], Malihi Z[1], Stewart AW[1], Lawes CM[1], Scragg R[1].

Public Health Nutr. **2018 Aug**;21(11):2022-2037. doi: 10.1017/S1368980018000551. PMID: 29559013. Epub 2018 Mar 21.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

OBJECTIVE: Pain-related conditions, such as chronic widespread pain and fibromyalgia, are major burdens for individuals and the health system. Evidence from previous research on the association between circulating 25-hydroxyvitamin D (25(OH)D) concentrations and pain is conflicting. Thus, we aimed to determine if there is an association between mean 25(OH)D concentration (primary aim), or proportion of hypovitaminosis D (secondary aim), and pain conditions in observational studies.

DESIGN: Published observational research on 25(OH)D concentration and pain-related conditions was systematically searched for in electronic sources (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) and a random-effects meta-analysis was conducted on included studies.

RESULTS: Eighty-one observational studies with a total of 50 834 participants were identified. Compared with controls, mean 25(OH)D concentration was significantly lower in patients with arthritis (mean difference (MD): -12·34 nmol/l; P<0·001), muscle pain (MD: -8·97 nmol/l; P=0·003) and chronic widespread pain (MD: -7·77 nmol/l; P<0·001), but not in patients with headache or migraine (MD: -2·53 nmol/l; P=0·06). The odds of vitamin D deficiency was increased for arthritis, muscle pain and chronic widespread pain, but not for headache or migraine, compared with controls. Sensitivity analyses revealed similar results.

CONCLUSIONS: A significantly lower 25(OH)D concentration was observed in patients with arthritis, muscle pain and chronic widespread pain, compared with those without. These results suggest that low 25(OH)D concentrations may be associated with pain conditions.

Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential.

Guo R[1], Chen LH[2], Xing C[3], Liu T[4].

Br J Anaesth. **2019 Sep 21**. pii: S0007-0912(19)30638-5. doi: 10.1016/j.bja.2019.07.026. PMID: 31551115.

The relationship between gut microbiota and neurological diseases, including chronic pain, has received increasing attention. The gut microbiome is a crucial modulator of visceral pain, whereas recent evidence suggests that gut microbiota may also play a critical role in many other types of chronic pain, including inflammatory pain, headache, neuropathic pain, and opioid tolerance. We present a narrative review of the current understanding on the role of gut microbiota in pain regulation and discuss the possibility of targeting gut microbiota for the management of chronic pain. Numerous signalling molecules derived from gut microbiota, such as by-products of microbiota, metabolites, neurotransmitters, and neuromodulators, act on their receptors and remarkably regulate the peripheral and central sensitisation, which in turn mediate the development of chronic pain. Gut microbiota-derived mediators serve as critical modulators for the induction of peripheral sensitisation, directly or indirectly regulating the excitability of primary nociceptive neurones. In the central nervous system, gut microbiota-derived mediators may regulate neuroinflammation, which involves the activation of cells in the blood-brain barrier, microglia, and infiltrating immune cells, to modulate induction and maintenance of central sensitisation. Thus, we propose that gut microbiota regulates pain in the peripheral and central nervous system, and targeting gut microbiota by diet and pharmabiotic intervention may represent a new therapeutic strategy for the management of chronic pain.

CHRONIC PAIN (Continued)

A Systematic Review on the Effects of Group Singing on Persistent Pain in People with Long-term Health Conditions.

Irons JY[1,2], Sheffield D[3], Ballington F[4], Stewart DE[5].

Eur J Pain. **2019 Sep 23**. doi: 10.1002/ejp.1485. PMID: 31549451. [Epub ahead of print]

BACKGROUND AND OBJECTIVES: Singing can have a range of health benefits; this paper reviews evidence of the effects of group singing for chronic pain in people with long-term health conditions.

DATABASE AND DATA TREATMENT: We searched for published peer-reviewed singing studies reporting pain measures (intensity, interference and depression) using major electronic databases (last search date 31/07/2018). After screening 123 full texts, 13 studies met the inclusion criteria: five RCTs, seven non-RCTs and one qualitative study. Included studies were appraised using Downs and Black and CASP quality assessments.

RESULTS: Included studies reported differences in the type of singing intervention, long-term condition and pain measures. Due to the high heterogeneity, we conducted a narrative review. There is a positive trend of singing interventions reducing pain intensity, but more equivocal support for reductions in pain interference and depression. Additionally, qualitative data synthesis identified three key linked and complementary themes: physical, psychological and social benefits.

CONCLUSION: Group singing appears to have potential to reduce pain intensity, pain interference and depression; however, we conclude there is only partial support for singing on some pain outcomes based on the limited available evidence of varied quality. Given the positive findings of qualitative studies, this review recommends that practitioners are encouraged to continue this work. More studies of better quality are needed. Future studies should adopt more robust methodology and report their singing intervention in details. Group singing may be an effective and safe approach for reducing persistent pain and depression in people with long-term health conditions.

Decision-Centered Design of Patient Information Visualizations to Support Chronic Pain Care.

Harle CA[1], Dilulio J[2], Downs SM[1], Danielson EC[1], Anders S[3], Cook RL[4], Hurley RW[5], Mamlin BW[6], Militello LG[2].

Appl Clin Inform. **2019 Aug**;10(4):719-728. doi: 10.1055/s-0039-1696668. PMID: 31556075. Epub 2019 Sep 25.

BACKGROUND: For complex patients with chronic conditions, electronic health records (EHRs) contain large amounts of relevant historical patient data. To use this information effectively, clinicians may benefit from visual information displays that organize and help them make sense of information on past and current treatments, outcomes, and new treatment options. Unfortunately, few clinical decision support tools are designed to support clinical sensemaking.

OBJECTIVE: The objective of this study was to describe a decision-centered design process, and resultant interactive patient information displays, to support key clinical decision requirements in chronic noncancer pain care.

METHODS: To identify key clinical decision requirements, we conducted critical decision method interviews with 10 adult primary care clinicians. Next, to identify key information needs and decision support design seeds, we conducted a half-day multidisciplinary design workshop. Finally, we designed an interactive prototype to support the key clinical decision requirements and information needs uncovered during the previous research activities.

RESULTS: The resulting Chronic Pain Treatment Tracker prototype summarizes the current treatment plan, past treatment history, potential future treatments, and treatment options to be cautious about. Clinicians can access additional details about each treatment, current or past, through modal views. Additional decision support for potential future treatments and treatments to be cautious about is also provided through modal views.

CONCLUSION: This study designed the Chronic Pain Treatment Tracker, a novel approach to decision support that presents clinicians with the information they need in a structure that promotes quick uptake, understanding, and action.

IRRITABLE BOWEL SYNDROME

Elucidating the putative link between prefrontal neurotransmission, functional connectivity, and affective symptoms in irritable bowel syndrome.

Icenhour A[1,2,3], Tapper S[4,5], Bednarska O[6], Witt ST[4], Tisell A[4,7,8], Lundberg P[4,7,8], Elsenbruch S[9], Walter S[6,4].

Sci Rep. **2019 Sep 19**;9(1):13590. doi: 10.1038/s41598-019-50024-3. PMCID: PMC6753205. PMID: 31537890.

Altered neural mechanisms are well-acknowledged in irritable bowel syndrome (IBS), a disorder of brain-gut-communication highly comorbid with anxiety and depression. As a key hub in corticolimbic inhibition, medial prefrontal cortex (mPFC) may be involved in disturbed emotion regulation in IBS. However, aberrant mPFC excitatory and inhibitory neurotransmission potentially contributing to psychological symptoms in IBS remains unknown. Using quantitative magnetic resonance spectroscopy (qMRS), we compared mPFC glutamate + glutamine (Glx) and γ-aminobutyric acid (GABA+) concentrations in 64 women with IBS and 32 age-matched healthy women (HCs) and investigated their association with anxiety and depression in correlational and subgroup analyses. Applying functional magnetic resonance imaging (fMRI), we explored whether altered neurotransmission was paralleled by aberrant mPFC resting-state functional connectivity (FC). IBS patients did not differ from HCs with respect to mPFC GABA+ or Glx levels. Anxiety was positively associated with mPFC GABA+ concentrations in IBS, whereas Glx was unrelated to psychological or gastrointestinal symptoms. Subgroup comparisons of patients with high or low anxiety symptom severity and HCs revealed increased GABA+ in patients with high symptom severity, and lower mPFC FC with adjacent anterior cingulate cortex (ACC), a crucial region of emotion modulation. Our findings provide novel evidence that altered prefrontal inhibitory neurotransmission may be linked to anxiety in IBS.

Faecal microbiota transplantation for diarrhoea-predominant irritable bowel syndrome: a double-blind, randomised, placebo-controlled trial.

Aroniadis OC[1], Brandt LJ[2], Oneto C[3], Feuerstadt P[4], Sherman A[3], Wolkoff AW[2], Kassam Z[5], Sadovsky RG[5], Elliott RJ[6], Budree S[7], Kim M[8], Keller MJ[2].

Lancet Gastroenterol Hepatol. **2019 Sep**;4(9):675-685. doi: 10.1016/S2468-1253(19)30198-0. PMID: 31326345. Epub 2019 Jul 17.

BACKGROUND: Faecal microbiota transplantation (FMT) has shown promise in alleviating the symptoms of irritable bowel syndrome (IBS); however, controlled data on this technique are scarce. The aim of this clinical trial was to assess the efficacy of FMT in alleviating diarrhoea-predominant IBS (IBS-D).

METHODS: We did a double-blind, randomised, placebo-controlled crossover trial in patients aged 18-65 years with moderate-to-severe IBS-D defined by an IBS-Symptom Severity Score (IBS-SSS) of more than 175, recruited from three US centres. Patients were randomly assigned (1:1) in blocks of four with a computer-generated randomisation sequence to receive FMT capsules followed by identical-appearing placebo capsules, or placebo capsules followed by FMT capsules. All participants and study team members were masked to randomisation. An independent staff member assigned the treatments according to consecutive numbers. Patients received either 75 FMT capsules (each capsule contained approximately 0·38 g of minimally processed donor stool) or 75 placebo capsules over 3 days (25 capsules per day). All patients crossed over to the alternate treatment at 12 weeks. The primary outcome was difference in IBS-SSS between the groups at 12 weeks. Intention-to-treat analyses were done and all patients who received study drug were included in an adverse events analysis. The trial was terminated during recruitment because results from an interim analysis revealed futility. The study is registered with ClinicalTrials.gov, number NCT02328547.

FINDINGS: From May 28, 2015, to April 21, 2017, 48 patients were randomly assigned to receive FMT first (n=25) or placebo first (n=23). Three participants were lost to follow-up in the FMT group. IBS-SSS did not differ between FMT recipients (mean 221 [SD 105]) and placebo recipients (236 [95]) at 12 weeks (p=0·65), after adjustment for baseline scores. The most common drug-related adverse events included abdominal pain (five [10%] of the 48 participants while receiving FMT capsules vs four [8%] while receiving placebo), nausea (four [8%] vs two [4%]), and exacerbation of diarrhoea (three [6%] vs eight [17%]). One serious adverse event that was unrelated to study drug (acute cholecystitis) was reported in a patient while receiving placebo capsules.

INTERPRETATION: FMT was safe, but did not induce symptom relief at 12 weeks compared with placebo. Additional studies are needed to determine the efficacy of FMT for IBS-D.

FUNDING: National Institutes of Health.

IRRITABLE BOWEL SYNDROME (Continued)

Lower socioeconomic status is associated with an increased prevalence of comorbid anxiety and depression among patients with irritable bowel syndrome: results from a multicenter cohort.

Silvernale C[1], Kuo B[1,2], Staller K[1,2,3].

Scand J Gastroenterol. **2019 Sep**;54(9):1070-1074. doi: 10.1080/00365521.2019.1665095. PMID: 31530048. Epub 2019 Sep 18.

Background/Aims: Anxiety and depression are common comorbid psychiatric disorders in IBS patients, but the population-level determinants influencing these comorbidities in IBS patients are poorly understood. We sought to determine whether there was an association between comorbid affective disorders and socioeconomic status among irritable bowel syndrome (IBS) patients.

Methods: We assembled a retrospective cohort of 1074 IBS patients with comorbid Generalized Anxiety Disorder (GAD) and/or Major Depressive Disorder (MDD) seen at two tertiary referral centers between 2007 and 2015. IBS patients with comorbid GAD and/or MDD were matched 3:1 by age, sex, and race to controls with IBS and no history of comorbid GAD and/or MDD. Socioeconomic status was approximated by patient zip codes.

Results: IBS patients in the lowest socioeconomic group were more likely to be diagnosed with GAD and/or MDD compared to controls (OR = 1.38, p = .0004). The median average per capita income for comorbid GAD/MDD IBS patient cohort was also significantly lower than the control IBS patient cohort ($39,880.50 vs. $41,277.00, p = .02).

Conclusions: Among IBS patients, the presence of comorbid Generalized Anxiety Disorder and/or Major Depressive Disorder is associated with lower socioeconomic status and lower average per capita income. These findings speak to a biopsychosocial model of illness, which should be considered by clinicians in the care of IBS patients.

Glutamine Blocks Interleukin-13-Induced Intestinal Epithelial Barrier Dysfunction.

Li M[1,2], Oshima T[3], Ito C[1], Yamada M[1], Tomita T[1], Fukui H[1], Miwa H[1].

Digestion. **2019 Sep 18**:1-10. doi: 10.1159/000502953. PMID: 31533100. [Epub ahead of print]

INTRODUCTION: Impaired intestinal epithelial barrier function is a hallmark of a variety of pathological conditions such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). IBD patients with IBS-like symptoms show higher interleukin-13 (IL-13) serum levels and poor psychological well-being. Supplementary glutamine reduced the daily bowel movement frequency, improved the stool form, and normalized intestinal hyperpermeability. This study was aimed at assessing the effects of IL-13 and supplementary glutamine on human intestinal epithelial function in vitro.

METHODS: Caco-2 cells were grown on TranswellTM inserts. -IL-13 was added to the basolateral compartment, and transepithelial electrical resistance (TEER) and fluorescein isothiocyanate (FITC) labeled-dextran permeability measured. Effects of glutamine or the phosphatidylinositol-3-kinase inhibitor LY294002 were assessed. Involvement of tight junction proteins was assessed using Western blotting and immunofluorescence staining.

RESULTS: IL-13 significantly decreased TEER and increased FITC labeled-dextran epithelial permeability. IL-13 stimulation decreased the claudin-1 expression and increased the claudin-2 expression. Glutamine alleviated IL-13-induced decrease of TEER and increase of FITC labeled-dextran permeability. Further, the phosphatidylinositol-3-kinase inhibitor showed this alleviating effect while the signal transducer and activator of transcription 6 inhibitor did not.

CONCLUSIONS: IL-13 induced barrier integrity impairment by decreasing claudin-1 and increasing claudin-2. Glutamine alleviated IL-13-induced barrier dysfunction by increasing claudin-1 expression, via disruption of the phosphatidylinositol-3-kinase/Akt signaling pathway.

IRRITABLE BOWEL SYNDROME (Continued)

Trimebutine: a state-of-the-art review.

Salvioli B[1,2].

Minerva Gastroenterol Dietol. **2019 Sep**;65(3):229-238. doi: 10.23736/S1121-421X.19.02567-4. PMID: 31617696.

Trimebutine maleate has been used extensively, since the late 1960's, for the treatment of functional gastrointestinal disorders, including irritable bowel syndrome (IBS). It is usually linked to the antispasmodic class of agents, but its properties make trimebutine an unmatched and multi-tasking compound. The efficacy on relieving abdominal pain has been demonstrated in various clinical studies with different protocols of treatment. The main effect was first believed to be merely due to its antispastic activity, but further evidences expanded the acknowledgement of a broader impact on the gastrointestinal tract. The actions of trimebutine are mediated via an agonist effect on peripheral mu, kappa and delta opiate receptors and a modulation of gastrointestinal peptides release. The final motor effects on the gut are summarized in an acceleration of the gastric emptying, an induction of premature phase III of the migrating motor complex in the small intestine and a modulation of the contractile activity of the colon. Moreover, it has been shown to have a role in regulating the visceral sensitivity. It has been observed that this drug is also a multiple-ion channel modulator in the gut. Its function at various levels, from motility to pain control, makes this drug unique and its spectrum of action can be exploited for the treatment of both hypermotility and hypomotility disorders including irritable bowel syndrome and other functional gastrointestinal diseases. This article provides an overview of the current knowledge on the pharmacological mechanisms of trimebutine and its clinical applications in gastrointestinal disorders. Its biochemical properties and the complex mechanisms of action, along with a well-studied pharmacological safety, make this compound still actual and valuable.

OTHER RESEARCH OF INTEREST

An Approach to Evaluate the Effects of Concomitant Prescribing of Opioids and Benzodiazepines on Veteran Deaths and Suicides.

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Developing a Protocol to Evaluate the Concomitant Prescribing of Opioids and Benzodiazepine Medications and Veteran Deaths and Suicides.

Washington (DC): National Academies Press (US); **2019 Sep**. https://doi.org/10.17226/25532.

Opioid prescriptions for acute and chronic pain increased dramatically from the late 1990s into the current decade in both the civilian and the Department of Veterans Affairs and Department of Defense treatment environments. Similarly, prescriptions for benzodiazepines also increased significantly for anxiety and insomnia. Combinations of opioid and benzodiazepines have proven fatal when taken concurrently, with research demonstrating this phenomenon for nearly 40 years. This issue is exacerbated within the veteran population because of higher rates of pain, anxiety and other related health issues due to military life. An evaluation of the relationship between opioid and benzodiazepine medication practices at the VA is necessary to improve treatment for mental health and combat-related trauma for veterans.

An Approach to Evaluate the Effects of Concomitant Prescribing of Opioids and Benzodiazepines on Veteran Deaths and Suicides investigates the effects of opioid initiation and tapering strategies in the presence of benzodiazepines in veterans. This report explores neurobiology and the principles of addiction and tolerance, in addition to the current use of opioids and benzodiazepines for treating pain and anxiety in both the veteran and general population. It also provides a protocol to evaluate the relationship between opioid and benzodiazepine medication practices. This framework is a critical foundation for further research to improve concomitant opioid and benzodiazepine medication practices for veterans and the general population.

OTHER RESEARCH OF INTEREST (Continued)

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Adjunctive Pimavanserin in Patients With Major Depressive Disorder and an Inadequate Response to Therapy (CLARITY).

Fava M[1,2], Dirks B[3], Freeman MP[2], Papakostas GI[2], Shelton RC[4], Thase ME[5], Trivedi MH[6], Liu K[3], Stankovic S[3].

J Clin Psychiatry. **2019 Sep 24**;80(6). pii: 19m12928. doi: 10.4088/JCP.19m12928. PMID: 31556975.

OBJECTIVE: Pimavanserin is a 5-hydroxytryptamine-2A antagonist and inverse receptor agonist. This phase 2 study examined the efficacy and safety of pimavanserin as adjunctive therapy in patients with major depressive disorder (MDD).

METHODS: This was a multicenter, randomized, double-blind, placebo-controlled study in patients with DSM-5-defined MDD and an inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Using a 2-stage sequential parallel-comparison design, patients were initially randomized in a 3:1 ratio to placebo or pimavanserin added to ongoing SSRI or SNRI therapy; at 5 weeks, placebo nonresponders were re-randomized to placebo or pimavanserin for an additional 5 weeks. Key endpoints were change from baseline to the end of each stage in 17-item Hamilton Depression Rating Scale (HDRS-17) total score and Sheehan Disability Scale (SDS) score.

RESULTS: Between December 2016 and October 2018, 207 patients were randomized. For the prespecified pooled Sequential Parallel Comparison Design analyses of Stages 1 and 2, the least squares (LS) mean (SE) difference for the HDRS-17 total score was -1.7 (0.85) (P = .039) and for the SDS score was -0.8 (0.29) (P = .004). At week 5 of Stage 1, LS mean (SE) difference for pimavanserin versus placebo was significant for changes on the HDRS-17 (-4.0 [1.09], P = .0003) and SDS (-1.2 [0.40], P = .0036) with effect sizes of 0.626 and 0.498, respectively. Early and sustained separation of pimavanserin from placebo (P < .05) occurred at 1 week. The most common adverse events with pimavanserin were dry mouth, nausea, and headache.

CONCLUSIONS: Pimavanserin demonstrated robust efficacy in patients with MDD and an inadequate response to an SSRI or SNRI. Tolerability was consistent with previous experience.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT03018340.

Targeted transcriptional modulation with type I CRISPR-Cas systems in human cells.

Pickar-Oliver A[1,2], Black JB[1,2], Lewis MM[1,2], Mutchnick KJ[1,2], Klann TS[1,2], Gilcrest KA[1,2], Sitton MJ[1,2], Nelson CE[1,2], Barrera A[3], Bartelt LC[2,3], Reddy TE[2,3,4], Beisel CL[5,6,7], Barrangou R[8], Gersbach CA[9,10,11].

Nat Biotechnol. 2019 Dec;37(12):1493-1501. doi: 10.1038/s41587-019-0235-7. PMCID: PMC6893126. PMID: 31548729.

Epub **2019 Sep 23**.

Class 2 CRISPR-Cas systems, such as Cas9 and Cas12, have been widely used to target DNA sequences in eukaryotic genomes. However, class 1 CRISPR-Cas systems, which represent about 90% of all CRISPR systems in nature, remain largely unexplored for genome engineering applications. Here, we show that class 1 CRISPR-Cas systems can be expressed in mammalian cells and used for DNA targeting and transcriptional control. We repurpose type I variants of class 1 CRISPR-Cas systems from Escherichia coli and Listeria monocytogenes, which target DNA via a multi-component RNA-guided complex termed Cascade. We validate Cascade expression, complex formation and nuclear localization in human cells, and demonstrate programmable CRISPR RNA (crRNA)-mediated targeting of specific loci in the human genome. By tethering activation and repression domains to Cascade, we modulate the expression of targeted endogenous genes in human cells. This study demonstrates the use of Cascade as a CRISPR-based technology for targeted eukaryotic gene regulation, highlighting class 1 CRISPR-Cas systems for further exploration.

OTHER RESEARCH OF INTEREST (Continued)

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association.

Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, Jacobson TA, Engler MB, Miller M, Robinson JG, Blum CB, Rodriguez-Leyva D, de Ferranti SD, Welty FK; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology.

Circulation. **2019 Sep 17**;140(12):e673-e691. doi: 10.1161/CIR.0000000000000709. PMID: 31422671. Epub 2019 Aug 19.

Hypertriglyceridemia (triglycerides 200-499 mg/dL) is relatively common in the United States, whereas more severe triglyceride elevations (very high triglycerides, ≥500 mg/dL) are far less frequently observed. Both are becoming increasingly prevalent in the United States and elsewhere, likely driven in large part by growing rates of obesity and diabetes mellitus. In a 2002 American Heart Association scientific statement, the omega-3 fatty acids (n-3 FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were recommended (at a dose of 2-4 g/d) for reducing triglycerides in patients with elevated triglycerides. Since 2002, prescription agents containing EPA+DHA or EPA alone have been approved by the US Food and Drug Administration for treating very high triglycerides; these agents are also widely used for hypertriglyceridemia. The purpose of this advisory is to summarize the lipid and lipoprotein effects resulting from pharmacological doses of n-3 FAs (>3 g/d total EPA+DHA) on the basis of new scientific data and availability of n-3 FA agents. In treatment of very high triglycerides with 4 g/d, EPA+DHA agents reduce triglycerides by ≥30% with concurrent increases in low-density lipoprotein cholesterol, whereas EPA-only did not raise low-density lipoprotein cholesterol in very high triglycerides. When used to treat hypertriglyceridemia, n-3 FAs with EPA+DHA or with EPA-only appear roughly comparable for triglyceride lowering and do not increase low-density lipoprotein cholesterol when used as monotherapy or in combination with a statin. In the largest trials of 4 g/d prescription n-3 FA, non-high-density lipoprotein cholesterol and apolipoprotein B were modestly decreased, indicating reductions in total atherogenic lipoproteins. The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT (Reduction of Cardiovascular Events With EPA Intervention Trial), a randomized placebo-controlled trial of EPA-only in high-risk patients treated with a statin. The results of a trial of 4 g/d prescription EPA+DHA in hypertriglyceridemia are anticipated in 2020. We conclude that prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of 4 g/d (>3 g/d total EPA+DHA) are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.

Big Data, Big Tech, and Protecting Patient Privacy.

Cohen IG[1], Mello MM[2].

JAMA. **2019 Aug 9**. doi: 10.1001/jama.2019.11365. PMID: 31397838. [Epub ahead of print]

The market for patient data has never been more active. Technology companies, from startups to giants, are eager to access electronic health record (EHR) data to build the next generation of health-focused products. Medical artificial intelligence (AI) is particularly data-hungry; large, representative data sets hold promise for advancing not only AI companies' growth, but also the health of patients.[1] Companies' overtures to major hospitals about data sharing have highlighted legal and ethical uncertainties as to whether and how to undertake these relationships.

One such partnership is now being challenged in court. In June 2019, a patient sued the University of Chicago Medical Center and Google for alleged misuse of patient EHR data.[2] This Viewpoint discusses the case and what it signals about the need for thoughtful governance of data sharing between health care organizations and technology companies.

[See full text of this Viewpoint article in JAMA.]

OTHER RESEARCH OF INTEREST (Continued)

"It's All in Your Head"-Medicine's Silent Epidemic.

Burke MJ[1,2].

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It's all in your head" is a phrase sometimes said by physicians to patients presenting with symptoms unexplained by medical disease. As a neurologist specializing in neuropsychiatry, nothing bothers me more than overhearing medical colleagues proclaim this one-liner at the bedside or snicker about these patients during rounds. Unbeknownst to them, I also hear my patients' version of being on the other end of this phrase and find myself constantly trying to repair the damage that these words can cause. Whether physicians like to admit it or not, medically unexplained symptoms encompass a vast terrain of clinical practice. In neurology, these symptoms fall under functional neurological disorder, but every specialty has their own variants and favored terminologies (eg, chronic fatigue syndrome, fibromyalgia). The inadequate management of this segment of medicine represents a silent epidemic that is slowly eroding patient-physician relationships, perpetuating unnecessary disability, and straining health care resources.

The irony of "it's all in your head" is that although this phrase is often used inappropriately and dismissively, it is technically correct. The problem does indeed lie within the head. More specifically, it lies within the brain and its complex networks that we are just beginning to understand. Over the past 10 years, neuroimaging research studies have consistently identified brain abnormalities in patients with medically unexplained symptoms—yes, biologically based changes in the activity and connections of brain regions, such as the amygdala, prefrontal cortex, temporal-parietal junction, and other structures.[1] These brain circuit abnormalities provide physiological explanations for once mysterious links between regions implicated in emotional processing and the generation of "physical" symptoms (eg, pain, fatigue, weakness). Jean-Martin Charcot, MD, a famous 19th century French neurologist and early pioneer of this field, reportedly insisted that a "functional lesion" would be found when microscopes were sufficiently powerful.[2] Well, our microscopes are getting better, and we are now starting to see evidence of the predicted functional or software disruptions in the brain. We still do not fully understand what causes these software problems; however, recent research suggests a multifactorial etiology, including genetic predisposition, environmental risk factors (eg, childhood adverse events), and psychological stressors.[3]

Despite the growing scientific literature, there has been minimal shift in physician attitudes toward these patients. Physicians seem quite comfortable with the idea of structural brain lesions causing psychological symptoms, such as a frontal lobe stroke causing depression or a temporal lobe tumor causing delusions. However, the reverse causality of psychological factors (borne of the same substrates—neurotransmitters, neurons, and synaptic connections) leading to neurological or systemic symptoms is often hastily dismissed and remains highly stigmatized. Thus, many physicians either simply ignore these kinds of symptoms or wrongfully assume that patients are malingering.

[See full text of this Viewpoint article in JAMA Neurology.]

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