GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Association of chronic fatigue syndrome with premature telomere attrition.

Rajeevan MS[1], Murray J[2,3], Oakley L[2,4], Lin JS[2], Unger ER[2].

J Transl Med. **2018 Feb 27**;16(1):44. doi: 10.1186/s12967-018-1414-x. PMID: 29486769.

BACKGROUND: Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a severely debilitating condition of unknown etiology. The symptoms and risk factors of ME/CFS share features of accelerated aging implicated in several diseases. Using telomere length as a marker, this study was performed to test the hypothesis that ME/CFS is associated with accelerated aging.

METHODS: Participant (n = 639) data came from the follow-up time point of the Georgia CFS surveillance study. Using the 1994 CFS Research Case Definition with questionnaire-based subscale thresholds for fatigue, function, and symptoms, participants were classified into four illness groups: CFS if all criteria were met (n = 64), CFS-X if CFS with exclusionary conditions (n = 77), ISF (insufficient symptoms/fatigue) if only some criteria were met regardless of exclusionary conditions (n = 302), and NF (non-fatigued) if no criteria and no exclusionary conditions (n = 196). Relative telomere length (T/S ratio) was measured using DNA from whole blood and real-time PCR. General linear models were used to estimate the association of illness groups or T/S ratio with demographics, biological measures and covariates with significance set at $p < 0.05$.

RESULTS: The mean T/S ratio differed significantly by illness group ($p = 0.0017$); the T/S ratios in CFS (0.90 ± 0.03) and ISF (0.94 ± 0.02) were each significantly lower than in NF (1.06 ± 0.04). Differences in T/S ratio by illness groups remained significant after adjustment for covariates of age, sex, body mass index, waist-hip ratio, post-exertional malaise and education attainment. Telomere length was shorter by 635, 254 and 424 base pairs in CFS, CFS-X and ISF, respectively, compared to NF. This shorter telomere length translates to roughly 10.1-20.5, 4.0-8.2 and 6.6-13.7 years of additional aging in CFS, CFS-X and ISF compared to NF respectively. Further, stratified analyses based on age and sex demonstrated that the association of ME/CFS with short telomeres is largely moderated by female subjects < 45 years old.

CONCLUSIONS: This study found a significant association of ME/CFS with premature telomere attrition that is largely moderated by female subjects < 45 years old. Our results indicate that ME/CFS could be included in the list of conditions associated with accelerated aging. Further work is needed to evaluate the functional significance of accelerated aging in ME/CFS.

Infection Elicited Autoimmunity and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: An Explanatory Model.

Blomberg J[1], Gottfries CG[2], Elfaitouri A[3], Rizwan M[1], Rosén A[4].

Front Immunol. **2018 Feb 15**;9:229. doi: 10.3389/fimmu.2018.00229. PMCID: PMC5818468. eCollection 2018.

Myalgic encephalomyelitis (ME) often also called chronic fatigue syndrome (ME/CFS) is a common, debilitating, disease of unknown origin. Although a subject of controversy and a considerable scientific literature, we think that a solid understanding of ME/CFS pathogenesis is emerging. In this study, we compiled recent findings and placed them in the context of the clinical picture and natural history of the disease. A pattern emerged, giving rise to an explanatory model. ME/CFS often starts after or during an infection. A logical explanation is that the infection initiates an autoreactive process, which affects several functions, including brain and energy metabolism. According to our model for ME/CFS pathogenesis, patients with a genetic predisposition and dysbiosis experience a gradual development of B cell clones prone to autoreactivity. Under normal circumstances these B cell offsprings would have led to tolerance. Subsequent exogenous microbial exposition (triggering) can lead to comorbidities such as fibromyalgia, thyroid disorder, and orthostatic hypotension. A decisive infectious trigger may then lead to immunization against autoantigens involved in aerobic energy production and/or hormone receptors and ion channel proteins, producing postexertional malaise and ME/CFS, affecting both muscle and brain. In principle, cloning and sequencing of immunoglobulin variable domains could reveal the evolution of pathogenic clones. Although evidence consistent with the model accumulated in recent years, there are several missing links in it. Hopefully, the hypothesis generates testable propositions that can augment the understanding of the pathogenesis of ME/CFS.

HEADACHE and MIGRAINE

A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study).

Starling AJ[1], Tepper SJ[2], Marmura MJ[3], Shamim EA[4], Robbins MS[5], Hindiyeh N[6], Charles AC[7], Goadsby PJ[8], Lipton RB[5], Silberstein SD[3], Gelfand AA[9], Chiacchierini RP[10], Dodick DW[1].

Cephalalgia. **2018 Jan 1**:333102418762525. doi: 10.1177/0333102418762525. PMID: 29504483. [Epub ahead of print]

Objective: To evaluate the efficacy and tolerability of single pulse transcranial magnetic stimulation (sTMS) for the preventive treatment of migraine.

Background: sTMS was originally developed for the acute treatment of migraine with aura. Open label experience has suggested a preventive benefit. The objective of this trial was to evaluate the efficacy and tolerability of sTMS for migraine prevention.

Methods: The eNeura SpringTMS Post-Market Observational U.S. Study of Migraine (ESPOUSE) Study was a multicenter, prospective, open label, observational study. From December 2014 to March 2016, patients with migraine (n = 263) were consented to complete a 1 month baseline headache diary followed by 3 months of treatment. The treatment protocol consisted of preventive (four pulses twice daily) and acute (three pulses repeated up to three times for each attack) treatment. Patients reported daily headache status, medication use, and device use with a monthly headache diary. The primary endpoint, mean reduction of headache days compared to baseline, was measured over the 28-day period during weeks 9 to 12. The primary endpoint was compared to a statistically-derived placebo estimate (performance goal). Secondary endpoints included: 50% responder rate, acute headache medication consumption, HIT-6, and mean reduction in total headache days from baseline of any intensity.

Results: Of a total of 263 consented subjects, 229 completed a baseline diary, and 220 were found to be eligible based on the number of headache days. The device was assigned to 217 subjects (Safety Data Set) and 132 were included in the intention to treat Full Analysis Set. For the primary endpoint, there was a -2.75 ± 0.40 mean reduction of headache days from baseline (9.06 days) compared to the performance goal (-0.63 days) ($p < 0.0001$). The 50% responder rate of 46% (95% CI 37%, 56%) was also significantly higher ($p < 0.0001$) than the performance goal (20%). There was a reduction of -2.93 (5.24) days of acute medication use, headache impact measured by HIT-6, -3.1 (6.4) ($p < 0.0001$), and total headache days of any intensity -3.16 days (5.21) compared to the performance goal (-0.63 days) ($p < 0.0001$). The most common adverse events were lightheadedness (3.7%), tingling (3.2%), and tinnitus (3.2%). There were no serious adverse events.

Conclusions: This open label study suggests that sTMS may be an effective, well-tolerated treatment option for migraine prevention. Trial registration number NCT02357381.

Association of neurologist care with headache expenditures: A population-based, longitudinal analysis.

Ney JP[1,2], Sico JJ[3], Klein BC[4], Magliocco B[5], Callaghan BC[6], Esper GJ[7].

Cephalalgia. **2018 Jan 1**:333102418762572. doi: 10.1177/0333102418762572. PMID: 29504480. [Epub ahead of print]

Objective: To assess the association of neurologist ambulatory care with healthcare utilization and expenditure in headache.

Methods: This was a longitudinal cohort study from two-year duration panel data, pooled from 2002-2013, of adult respondents identified with diagnostic codes for headache in the Medical Expenditure Panel Survey. Those with a neurologist ambulatory care visit in year one of panel participation were compared with those who did not for the change in annual aggregate direct headache-related health care costs from year one to year two of panel participation, inflated to 2015 US dollars. Results were adjusted via multiple linear regression for demographic and clinical variables, utilizing survey variables for accurate estimates and standard errors.

Results: Eight hundred and eighty-seven respondents were included, with 23.3% (207/887) seeing a neurologist in year one. The neurologist group had higher year-one mean headache-related expenditures ($3032 vs. $1636), but nearly equal mean year-two expenditures compared to controls ($1900 vs. $1929). Adjusted association between neurologist care and difference in mean annual expenditures from year two to year one was -$1579 (95% CI -$2468, -$690, $p < 0.001$).

Conclusion: Among headache sufferers, particularly those with higher headache-related healthcare expenditures, neurologist care is associated with a significant reduction in costs over two years.

HEADACHE and MIGRAINE (Continued)

Deep in the brain: Changes in subcortical function immediately preceding a migraine attack.

Meylakh N[1], Marciszewski KK[1], Di Pietro F[1], Macefield VG[2], Macey PM[3], Henderson LA[1].

Hum Brain Mapp. **2018 Mar 2**. doi: 10.1002/hbm.24030. PMID: 29498776. [Epub ahead of print]

The neural mechanism responsible for migraine remains unclear. While the role of an external trigger in migraine initiation remains vigorously debated, it is generally assumed that migraineurs display altered brain function between attacks. This idea stems from relatively few brain imaging studies with even fewer studies exploring changes in the 24 h period immediately prior to a migraine attack. Using functional magnetic resonance imaging, we measured infra-slow oscillatory activity, regional homogeneity, and connectivity strengths of resting activity in migraineurs directly before (n = 8), after (n = 11), and between migraine attacks (n = 26) and in healthy control subjects (n = 78). Comparisons between controls and each migraine group and between migraine groups were made for each of these measures. Directly prior to a migraine, increased infra-slow oscillatory activity occurred in brainstem and hypothalamic regions that also display altered activity during a migraine itself, that is, the spinal trigeminal nucleus, dorsal pons, and hypothalamus. Furthermore, these midbrain and hypothalamic sites displayed increased connectivity strengths and regional homogeneity directly prior to a migraine. Remarkably, these resting oscillatory and connectivity changes did not occur directly after or between migraine attacks and were significantly different to control subjects. These data provide evidence of altered brainstem and hypothalamic function in the period immediately before a migraine and raise the prospect that such changes contribute to the expression of a migraine attack.

Localization of migraine susceptibility genes in human brain by single-cell RNA sequencing.

Renthal W[1].

Cephalalgia. **2018 Jan 1**:333102418762476. doi: 10.1177/0333102418762476. PMID: 29498289. [Epub ahead of print]

Background: Migraine is a debilitating disorder characterized by severe headaches and associated neurological symptoms. A key challenge to understanding migraine has been the cellular complexity of the human brain and the multiple cell types implicated in its pathophysiology. The present study leverages recent advances in single-cell transcriptomics to localize the specific human brain cell types in which putative migraine susceptibility genes are expressed.

Methods: The cell-type specific expression of both familial and common migraine-associated genes was determined bioinformatically using data from 2,039 individual human brain cells across two published single-cell RNA sequencing datasets. Enrichment of migraine-associated genes was determined for each brain cell type.

Results: Analysis of single-brain cell RNA sequencing data from five major subtypes of cells in the human cortex (neurons, oligodendrocytes, astrocytes, microglia, and endothelial cells) indicates that over 40% of known migraine-associated genes are enriched in the expression profiles of a specific brain cell type. Further analysis of neuronal migraine-associated genes demonstrated that approximately 70% were significantly enriched in inhibitory neurons and 30% in excitatory neurons.

Conclusions: This study takes the next step in understanding the human brain cell types in which putative migraine susceptibility genes are expressed. Both familial and common migraine may arise from dysfunction of discrete cell types within the neurovascular unit, and localization of the affected cell type(s) in an individual patient may provide insight into to their susceptibility to migraine.

CHRONIC PAIN

Identification of candidate genes associated with fibromyalgia susceptibility in southern Spanish women: the al-Ándalus project.

Estévez-López F[1,2], Camiletti-Moirón D[3], Aparicio VA[4], Segura-Jiménez V[3], Álvarez-Gallardo IC[3], Soriano-Maldonado A[5,6], Borges-Cosic M[7], Acosta-Manzano P[7], Geenen R[8], Delgado-Fernández M[7], Martínez-González LJ[9], Ruiz JR[10], Álvarez-Cubero MJ[9,11].

J Transl Med. **2018 Feb 27**;16(1):43. doi: 10.1186/s12967-018-1416-8. PMCID: PMC5828244. PMID: 29486785.

BACKGROUND: Candidate-gene studies on fibromyalgia susceptibility often include a small number of single nucleotide polymorphisms (SNPs), which is a limitation. Moreover, there is a paucity of evidence in Europe. Therefore, we compared genotype frequencies of candidate SNPs in a well-characterised sample of Spanish women with fibromyalgia and healthy non-fibromyalgia women.

METHODS: A total of 314 women with a diagnosis of fibromyalgia (cases) and 112 non-fibromyalgia healthy (controls) women participated in this candidate-gene study. Buccal swabs were collected for DNA extraction. Using TaqMan™ OpenArray™, we analysed 61 SNPs of 33 genes related to fibromyalgia susceptibility, symptoms, or potential mechanisms.

RESULTS: We observed that the rs841 and rs1799971 GG genotype was more frequently observed in fibromyalgia than in controls ($p = 0.04$ and $p = 0.02$, respectively). The rs2097903 AT/TT genotypes were also more often present in the fibromyalgia participants than in their control peers ($p = 0.04$). There were no differences for the remaining SNPs.

CONCLUSIONS: We identified, for the first time, associations of the rs841 (guanosine triphosphate cyclohydrolase 1 gene) and rs2097903 (catechol-O-methyltransferase gene) SNPs with higher risk of fibromyalgia susceptibility. We also confirmed that the rs1799971 SNP (opioid receptor μ1 gene) might confer genetic risk of fibromyalgia. We did not adjust for multiple comparisons, which would be too stringent and yield to non-significant differences in the genotype frequencies between cases and controls. Our findings may be biologically meaningful and informative, and should be further investigated in other populations. Of particular interest is to replicate the present study in a larger independent sample to confirm or refute our findings. On the other hand, by including 61 SNPs of 33 candidate-genes with a strong rationale (they were previously investigated in relation to fibromyalgia susceptibility, symptoms or potential mechanisms), the present research is the most comprehensive candidate-gene study on fibromyalgia susceptibility to date.

Telephone-based management of chronic pain in older adults in an integrated care program.

Helstrom A[1,2], Haratz J[3], Chen S[1], Benson A[1,2], Streim J[1,2], Oslin D[1,2].

Int J Geriatr Psychiatry. **2018 Mar 2**. doi: 10.1002/gps.4860. PMID: 29498774. [Epub ahead of print]

OBJECTIVE: Few studies have explored behavioral strategies for managing chronic pain in older adults. Pain Care Management (PCM) is a telephone-based behavioral intervention for chronic pain. The present study examined chronic pain characteristics among older adults and tested the delivery of PCM as an adjunct to depression and anxiety care management.

METHODS: Participants were drawn from a state-sponsored program offering care management services to community members aged 65 and older who were prescribed a psychotropic medication by a primary care provider. Chronic pain information was collected for all participants in the state program (N = 250) and treatment outcome data were collected for a subset with significant chronic pain. Eighty participants with high chronic pain interference were offered PCM and compared to 80 participants with chronic pain who received monitoring only on depression, anxiety, and pain interference outcomes.

RESULTS: Chronic pain was identified in 14% of older adults newly prescribed a psychotropic medication. Compared to monitoring only, PCM participants had higher odds of seeing a reduction of 2 or more points in pain interference at 6 months. Pain care management participants' anxiety scores significantly decreased over the study period.

CONCLUSIONS: Older adults treated with psychotropic medications often also experience chronic pain that interferes with daily activities. A telephone-based care management intervention is acceptable and feasible with an older community-based population and can lead to improvements in anxiety symptoms and interference from chronic pain. Further research will help to refine interventions that may help improve symptoms and increase functioning with this population.

CHRONIC PAIN (Continued)

Neuropsychological Functioning and Treatment Outcomes in Acceptance and Commitment Therapy for Chronic Pain.

Herbert MS[1], Afari N[2], Robinson JB[3], Listvinsky A[3], Bondi MW[4], Wetherell JL[4].

J Pain. **2018 Feb 26**. pii: S1526-5900(18)30088-9. doi: 10.1016/j.jpain.2018.02.008. PMID: 29496638. [Epub ahead of print]

Neuropsychological (NP) performance has been associated with psychosocial treatment outcomes in non-pain conditions, but has never been investigated in chronic pain. We performed a secondary analysis on the association of baseline NP performance with treatment outcomes among veterans with chronic pain (N = 117) undergoing an 8-week Acceptance and Commitment Therapy (ACT) intervention. Participants completed measures of pain interference, pain severity, quality of life, activity levels, depression, and pain-related anxiety at baseline, mid-treatment, and post-treatment. Executive functioning, working memory, processing speed, learning, and verbal memory were assessed at baseline. All study measures significantly improved from baseline to post-treatment. NP performance was related to changes in depression and pain-related anxiety during treatment. Specifically, relatively lower executive functioning and processing speed was associated with greater decreases in depressive symptoms, and relatively lower processing speed was associated with greater decreases in pain-related anxiety. Consistent with research in non-pain conditions, those with relatively lower NP functioning received greater benefit from psychosocial treatment, although the majority of study outcomes did not differ as a function of NP performance. Our results suggest relatively lower NP functioning is not contraindicated for participation in psychosocial interventions like ACT but instead may be associated with greater relief.

PERSPECTIVE: This study suggests that NP functioning is unrelated to changes in pain interference associated with ACT, and that those with relatively lower NP functioning may experience greater reductions in depressive symptoms and pain-related anxiety. This article contains important information for researchers and clinicians interested in cognition and chronic pain.

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia.

Welsch P[1], Üçeyler N, Klose P, Walitt B, Häuser W.

Cochrane Database Syst Rev. **2018 Feb 28**;2:CD010292. doi: 10.1002/14651858.CD010292.pub2. PMID: 29489029.

BACKGROUND: Fibromyalgia is a clinically defined chronic condition of unknown etiology characterized by chronic widespread pain that often co-exists with sleep disturbances, cognitive dysfunction and fatigue. People with fibromyalgia often report high disability levels and poor quality of life. Drug therapy, for example, with serotonin and noradrenaline reuptake inhibitors (SNRIs), focuses on reducing key symptoms and improving quality of life. This review updates and extends the 2013 version of this systematic review.

OBJECTIVES: To assess the efficacy, tolerability and safety of serotonin and noradrenaline reuptake inhibitors (SNRIs) compared with placebo or other active drug(s) in the treatment of fibromyalgia in adults.

SEARCH METHODS: For this update we searched CENTRAL, MEDLINE, Embase, the US National Institutes of Health and the World Health Organization (WHO) International Clinical Trials Registry Platform for published and ongoing trials and examined the reference lists of reviewed articles, to 8 August 2017.

SELECTION CRITERIA: We selected randomized, controlled trials of any formulation of SNRIs against placebo or any other active treatment of fibromyalgia in adults.

DATA COLLECTION AND ANALYSIS: Three review authors independently extracted data, examined study quality, and assessed risk of bias. For efficacy, we calculated the number needed to treat for an additional beneficial outcome (NNTB) for pain relief of 50% or greater and of 30% or greater, patient's global impression to be much or very much improved, dropout rates due to lack of efficacy, and the standardized mean differences (SMD) for fatigue, sleep problems, health-related quality of life, mean pain intensity, depression, anxiety, disability, sexual function, cognitive disturbances and tenderness. For tolerability we calculated number needed to treat for an additional harmful outcome (NNTH) for withdrawals due to adverse events and for nausea, insomnia and somnolence as specific adverse events. For safety we calculated NNTH for serious adverse events. We undertook meta-analysis using a random-effects model. We assessed the evidence using GRADE and created a 'Summary of findings' table.

CHRONIC PAIN (Continued)

Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. (Continued)

MAIN RESULTS: We added eight new studies with 1979 participants for a total of 18 included studies with 7903 participants. Seven studies investigated duloxetine and nine studies investigated milnacipran against placebo. One study compared desvenlafaxine with placebo and pregabalin. One study compared duloxetine with L-carnitine. The majority of studies were at unclear or high risk of bias in three to five domains. The quality of evidence of all comparisons of desvenlafaxine, duloxetine and milnacipran versus placebo in studies with a parallel design was low due to concerns about publication bias and indirectness, and very low for serious adverse events due to concerns about publication bias, imprecision and indirectness. The quality of evidence of all comparisons of duloxetine and desvenlafaxine with other active drugs was very low due to concerns about publication bias, imprecision and indirectness. Duloxetine and milnacipran had no clinically relevant benefit over placebo for pain relief of 50% or greater: 1274 of 4104 (31%) on duloxetine and milnacipran reported pain relief of 50% or greater compared to 591 of 2814 (21%) participants on placebo (risk difference (RD) 0.09, 95% confidence interval (CI) 0.07 to 0.11; NNTB 11, 95% CI 9 to 14). Duloxetine and milnacipran had a clinically relevant benefit over placebo in patient's global impression to be much or very much improved: 888 of 1710 (52%) on duloxetine and milnacipran (RD 0.19, 95% CI 0.12 to 0.26; NNTB 5, 95% CI 4 to 8) reported to be much or very much improved compared to 354 of 1208 (29%) of participants on placebo. Duloxetine and milnacipran had a clinically relevant benefit compared to placebo for pain relief of 30% or greater. RD was 0.10; 95% CI 0.08 to 0.12; NNTB 10, 95% CI 8 to 12. Duloxetine and milnacipran had no clinically relevant benefit for fatigue (SMD -0.13, 95% CI -0.18 to -0.08; NNTB 18, 95% CI 12 to 29), compared to placebo. There were no differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD -0.07; 95 % CI -0.15 to 0.01). Duloxetine and milnacipran had no clinically relevant benefit compared to placebo in improving health-related quality of life (SMD -0.20, 95% CI -0.25 to -0.15; NNTB 11, 95% CI 8 to 14). There were 794 of 4166 (19%) participants on SNRIs who dropped out due to adverse events compared to 292 of 2863 (10%) of participants on placebo (RD 0.07, 95% CI 0.04 to 0.10; NNTH 14, 95% CI 10 to 25). There was no difference in serious adverse events between either duloxetine, milnacipran or desvenlafaxine and placebo (RD -0.00, 95% CI -0.01 to 0.00). There was no difference between desvenlafaxine and placebo in efficacy, tolerability and safety in one small trial. There was no difference between duloxetine and desvenlafaxine in efficacy, tolerability and safety in two trials with active comparators (L-carnitine, pregabalin).

AUTHORS' CONCLUSIONS: The update did not change the major findings of the previous review. Based on low- to very low-quality evidence, the SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in the frequency of pain relief of 50% or greater, but for patient's global impression to be much or very much improved and in the frequency of pain relief of 30% or greater there was a clinically relevant benefit. The SNRIs duloxetine and milnacipran provided no clinically relevant benefit over placebo in improving health-related quality of life and in reducing fatigue. Duloxetine and milnacipran did not significantly differ from placebo in reducing sleep problems. The dropout rates due to adverse events were higher for duloxetine and milnacipran than for placebo. On average, the potential benefits of duloxetine and milnacipran in fibromyalgia were outweighed by their potential harms. However, a minority of people with fibromyalgia might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran. We did not find placebo-controlled studies with other SNRIs than desvenlafaxine, duloxetine and milnacipran.

OTHER RESEARCH OF INTEREST

VA Partners With DeepMind to Build Machine Learning Tools to Identify Health Risks for Veterans

February 21, 2018: News Release—Washington, DC, U.S. Department of Veterans Affairs, Office of Public Affairs Media Relations

Today the Department of Veterans Affairs (VA) announced that it has approved a medical research partnership with DeepMind to address the global issue of patient deterioration during hospital care, which accounts for 11 percent of in-hospital deaths around the world.

The partnership will focus on analyzing patterns from approximately 700,000 historical, de-personalized health records to develop machine learning algorithms that will accurately identify risk factors for patient deterioration and predict its onset. Initial work will be focused on identifying the most common signs of risk, like acute kidney injury, a problem that can lead to dialysis or death, but is preventable if detected early.

“Medicine is more than treating patients’ problems,” said VA Secretary David J. Shulkin. “Clinicians need to be able to identify risks to help prevent disease. This collaboration is an opportunity to advance the quality of care for our nation’s Veterans by predicting deterioration and applying interventions early.”

Eventually, similar approaches will be applied to other signs of patient deterioration, leading to improved care for many more patients, with fewer people developing serious infections and conditions — ultimately saving lives. “We are proud to partner with the Department of Veterans Affairs on this important challenge,” said Mustafa Suleyman, co-founder of DeepMind. “This project has great potential intelligently to detect and prevent deterioration before patients show serious signs of illness. Speed is vital when a patient is deteriorating: The sooner the right information reaches the right clinician, the sooner the patient can be given the right care.”

DeepMind is the world leader in artificial intelligence research. It has already partnered with leading hospitals in the United Kingdom to apply its innovative machine-learning algorithms to research projects looking at eye disease, head and neck cancer, and mammography.

Significance of risk polymorphisms for depression depends on stress exposure.

Gonda X[1,2,3], Hullam G[4,5], Antal P[5], Eszlari N[4,6], Petschner P[4,7], Hökfelt TG[8], Anderson IM[9,10], Deakin JFW[9,10,11], Juhasz G[4,7,9,10,12], Bagdy G[4,7,6].

Sci Rep. **2018 Mar 2**;8(1):3946. doi: 10.1038/s41598-018-22221-z. PMID: 29500446.

Depression is a polygenic and multifactorial disorder where environmental effects exert a significant impact, yet most genetic studies do not consider the effect of stressors which may be one reason for the lack of replicable results in candidate gene studies, GWAS and between human studies and animal models. Relevance of functional polymorphisms in seven candidate genes previously implicated in animal and human studies on a depression-related phenotype given various recent stress exposure levels was assessed with Bayesian relevance analysis in 1682 subjects. This Bayesian analysis indicated a gene-environment interaction whose significance was also tested with a traditional multivariate analysis using general linear models. The investigated genetic factors were only relevant in the moderate and/or high stress exposure groups. Rank order of genes was GALR2 > BDNF > P2RX7 > HTR1A > SLC6A4 > CB1 > HTR2A, with strong relevance for the first four. Robust gene-gene-environment interaction was found between BDNF and HTR1A. Gene-environment interaction effect was confirmed, namely no main effect of genes, but a significant modulatory effect on environment-induced development of depression were found. Our data support the strong causative role of the environment modified by genetic factors, similar to animal models. Gene-environment interactions point to epigenetic factors associated with risk SNPs. Galanin-2 receptor, BDNF and X-type purin-7 receptor could be drug targets for new antidepressants.

OTHER RESEARCH OF INTEREST (Continued)

Outcomes.

Leucht S[1], Davis JM[2,3].

JAMA Psychiatry. **2018 Feb 28**. doi: 10.1001/jamapsychiatry.2017.4704. PMID: 29490368. [Epub ahead of print]

Editorial Comment on Original Investigation:
the Prevention of Rehospitalization in a Finnish Nationwide Cohort of Patients With Bipolar Disorder. JAMA Psychiatry. 2018 Feb 28. doi: 10.1001/jamapsychiatry.2017.4711. PMID: 29490359

Lähteenvuo et al present an analysis of Finnish national registers with the question of which psychotropic drugs reduce the need for rehospitalization in people with bipolar disorder. Psychiatry is currently seeing a wave of such analyses, which, in part, might reflect the limitations of randomized clinical trials (RCTs). While RCTs are considered to be the gold standard because only randomization can rule out both known and unknown confounders, their limitations include trial populations that are not representative of the real world, trials that are typically short term, and outcomes that, in RCTs focused on the maintenance of patients with chronic disease, include only worsening of symptoms rather than full-blown rehospitalization. The analyses of national cohorts overcome these problems by examining all patients in 1 country who are followed up for several years, who can then contribute to very large sample sizes.

But these cohort studies are not without limitations. In his presidential address to the Royal Society of Medicine, Sir Austin Bradford Hill came up with the following criteria (also known as Hill's postulates) to decide which findings are valid: (1) strength, (2) consistency, (3) specificity, (4) temporality (with a cause occurring before the effect), (5) biologic gradient (dose-response relationship), (6) plausibility, (7) coherence, (8) experimental controlled studies (if such exist), and (9) analogy. Some of these can also be applied to the current analysis.

A major limitation is that analyses of national registers can never fully control for confounders. For example, classic mood stabilizers were more effective than antipsychotics for the prevention of rehospitalization. This could be an example for "confounding by indication," as the authors nicely explain: "the fact that treatments for individual patients are not selected at random, but are rather products of comprehensive clinical decision-making, the reasons for which are not stored in basic registries." In other words, a change in outcome might reflect something associated with the reason the drug was used. Thus, it could be that the more patients with milder cases of bipolar disorder received mood stabilizers, while severely ill patients received antipsychotic medications. Theoretically, if most patients had initially received lithium, and if antipsychotics had mainly been added to the medication regimens of patients with poor outcomes who had relapsed, this would be a disadvantage for antipsychotics. The applied within-subject approach in which patients are compared with their own previous treatment, rather than with other patients, is superior to conventional between-subject approaches and partly controls for this problem. But there are multiple imaginable clinical scenarios in terms of the sequence of drugs used, and there are multiple possible combinations of drugs (eFigure 1 in the Supplement of Lähteenvuo et al shows only 2 examples). Each combination of drugs must be accounted for statistically, but statistics have their limitations—and not all sensitivity analyses agreed with the primary analysis.

We would also caution against interpretation of findings without considering the events and years at risk. For example, for mood stabilizers, there were 21 054 events and 63 139 years at risk, whereas the long-acting injectable antipsychotic olanzapine had 6 events and 11 years at risk (per eTable 3 in the Supplement of Lähteenvuo et al). Gabapentin, which had 176 events and 541 years at risk, does not have an official indication for bipolar disorder, but had a high effect size. It could be that gabapentin was used for general medical reasons and thus used selectively for patients who were doing well, whereas benzodiazepines, which had a poor outcome, were added during episodes of more severe illness for sedation. [Full text of JAMA Psychiatry Editorial.]

OTHER RESEARCH OF INTEREST (Continued)

cluster analysis of six variables.

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BACKGROUND: Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.

METHODS: We did data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly diagnosed diabetes (n=8980) from the Swedish All New Diabetics in Scania cohort. Clusters were based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance), and were related to prospective data from patient records on development of complications and prescription of medication. Replication was done in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485). Cox regression and logistic regression were used to compare time to medication, time to reaching the treatment goal, and risk of diabetic complications and genetic associations.

FINDINGS: We identified five replicable clusters of patients with diabetes, which had significantly different patient characteristics and risk of diabetic complications. In particular, individuals in cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In support of the clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

INTERPRETATION: We stratified patients into five subgroups with differing disease progression and risk of diabetic complications. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

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