GULF WAR ILLNESS

Exploring the Diagnostic Potential of Immune Biomarker Co-expression in Gulf War Illness.

Broderick G[1,2], Fletcher MA[3,4], Gallagher M[5], Barnes Z[3,6], Vernon SD[7], Klimas NG[4,8].

Methods Mol Biol. **2018**;1781:101-120. doi: 10.1007/978-1-4939-7828-1_7. PMID: 29705845.

Complex disorders like Gulf War illness (GWI) often defy diagnosis on the basis of a single biomarker and may only be distinguishable by considering the co-expression of multiple markers measured in response to a challenge. We demonstrate the practical application of such an approach using an example where blood was collected from 26 GWI, 13 healthy control subjects, and 9 unhealthy controls with chronic fatigue at three points during a graded exercise challenge. A 3-way multivariate projection model based on 12 markers of endocrine and immune function was constructed using a training set of n = 10 GWI and n = 11 healthy controls. These groups were separated almost completely on the basis of two co-expression patterns. In a separate test set these same features allowed for discrimination of new GWI subjects (n = 16) from unhealthy (n = 9) and healthy control subjects with a sensitivity of 70% and a specificity of 90%.

CHRONIC FATIGUE SYNDROME

Robuvit®: improvement of fatigue in medical convalescence.

Ippolito E[1,2,3], Belcaro G[4,2,3,5], Luzzi R[1], Hosoi M[1], Dugall M[1], Rohdewald P[2], Feragalli B[1], Cotellese R[1], Peterzan P[1].

J Sports Med Phys Fitness. **2018 May**;58(5):678-683. doi: 10.23736/S0022-4707.17.08158-0. PMID: 29719945.

BACKGROUND: The aim of this registry study was the evaluation of symptoms of fatigue following supplementation with an oak wood extract (Robuvit®) after disappearance of acute symptoms. Robuvit®, with established antioxidant-antifatigue activity, has been successfully used in hepatic failure and in chronic fatigue syndrome: these conditions are characterized by weakness and fatigue and are broadly comparable to convalescence that is associated to increased oxidative stress.

METHODS: The registry study lasted 3 weeks. After a period (7-10 days) of flu, during the post-disease period (3 days without disease) subjects were included into the study. One group of subjects was supplemented with Robuvit® (300 mg/day) in addition to a standard management (SM) plan, another group of patients was treated with the standard management only.

RESULTS: The SM and the supplement group were comparable in all convalescence parameters at inclusion. Weakness and heart rate were significantly reduced with Robuvit® in comparison with the controls (P<0.05) at 10 days and at 3 weeks; Attention and sleep patterns improved significantly at 3 weeks with Robuvit® (P<0.05) in comparison to controls. Recovery after efforts was normalized at 10 days in the supplement group, significantly better versus controls (P<0.05). O2 saturation increased significantly with Robuvit® at 10 days in comparison to controls (P<0.05). The alterations in working/concentration capacity were better improved with the supplement (P<0.05). Oxidative stress was significantly decreased (P<0.05) in comparison to controls. The improvement of health according to the Karrnofsky Scale was significantly more pronounced in the Robuvit® group (P<0.05). The supplement was well tolerated.

CONCLUSIONS: The causative relations between Robuvit® supplementation, oxidative stress, vigor and fatigue in convalescence need more specific evaluations in a larger number of subjects. This preliminary study may indicate a possible supplementation in convalescence.

HEADACHE and MIGRAINE

Assessing Physician-Patient Dialogues About Chronic Migraine During Routine Office Visits.

Buse DC[1], Gillard P[2], Arctander K[3], Kuang AW[2], Lipton RB[1].

Headache. **2018 May 4**. doi: 10.1111/head.13314. PMID: 29727478. [Epub ahead of print].

OBJECTIVE: To assess physician-patient communication and identify the frequency of use of specific communication techniques by analyzing recordings of routinely scheduled medical encounters for patients with clinician-identified chronic migraine.

BACKGROUND: Chronic migraine is an under-diagnosed, under-treated, and highly burdensome disease. Effective medical communication is integral to optimal medical care, including providing accurate diagnoses, creating effective treatment plans, and enhancing patient adherence. Communication patterns during office visits may be a target for intervention to improve outcomes for people with chronic migraine.

DESIGN: This was a prospective, observational study based on analysis of audio recordings collected during neurologist-patient chronic migraine dialogues.

METHODS: Twenty neurologists from a US neurology panel maintained by Verilogue, Inc., a research organization specializing in healthcare dialogues, were invited to identify patients with chronic migraine and record clinical encounters with their patients. Both new patient visits and follow-up visits were included in this analysis. Neurologist-patient dialogues were audio-recorded, anonymized, transcribed, and analyzed by a sociolinguist for the presence of prespecified communication parameters, strategies, and specific language indicative of optimal migraine-related medical care.

RESULTS: Fourteen out of the 20 invited neurologists (70.0%) accepted the study invitation and recorded 35 encounters with patients eligible for the study. The patient sample was 91.4% female (n = 32/35), with a mean age of 46 years. On average, there were 17 headache-related questions per visit; 82.0% of questions were closed-ended (n = 369/450). Headache/migraine frequency was elicited in 77.1% of the dialogues (n = 27/35), but headache days per month was assessed in only a single dialogue. Only one neurologist utilized the ask-tell-ask technique. Headache-related disability was discussed in 22.9%of the dialogues (n = 8/35), with only one using open-ended questions. None of the dialogues discussed ictal vs interictal headache-related disability. Chronic migraine was mentioned in 8.6% of dialogues (n = 3/35) and treatment plans were discussed in 37.1% of the dialogues (n = 13/35).

CONCLUSIONS: Results from this preliminary study showed that the majority of the neurologist-chronic migraine patient dialogues did not assess elements crucial for diagnosis and treatment (eg, headache days per month and headache related disability) or use standard communication techniques (eg, open-ended questions, ask-tell-ask). We recommend intervention studies designed to assess the benefits of improved communication on diagnostic accuracy, treatment decisions, and patient reported outcomes.

Human local adaptation of the TRPM8 cold receptor along a latitudinal cline.

Key FM[1,2], Abdul-Aziz MA[1], Mundry R[3], Peter BM[4], Sekar A[5], D'Amato M[6], Dennis MY[5], Schmidt JM[1], Andrés AM[1,7].

PLoS Genet. **2018 May 3**;14(5):e1007298. doi: 10.1371/journal.pgen.1007298. PMID: 29723195. eCollection 2018 May.

Ambient temperature is a critical environmental factor for all living organisms. It was likely an important selective force as modern humans recently colonized temperate and cold Eurasian environments. Nevertheless, as of yet we have limited evidence of local adaptation to ambient temperature in populations from those environments. To shed light on this question, we exploit the fact that humans are a cosmopolitan species that inhabit territories under a wide range of temperatures. Focusing on cold perception-which is central to thermoregulation and survival in cold environments-we show evidence of recent local adaptation on TRPM8. This gene encodes for a cation channel that is, to date, the only temperature receptor known to mediate an endogenous response to moderate cold. The upstream variant rs10166942 shows extreme population differentiation, with frequencies that range from 5% in Nigeria to 88% in Finland (placing this SNP in the 0.02% tail of the FST empirical distribution). When all populations are jointly analyzed, allele frequencies correlate with latitude and temperature beyond what can be explained by shared ancestry and population substructure. Using a Bayesian approach, we infer that the allele originated and evolved neutrally in Africa, while positive selection raised its frequency to different degrees in Eurasian populations, resulting in allele frequencies that follow a latitudinal cline. We infer strong positive selection, in agreement with ancient DNA showing high frequency of the allele in Europe 3,000 to 8,000 years ago. rs10166942 is important phenotypically because its ancestral allele is protective of migraine. This debilitating disorder varies in prevalence across human populations, with highest prevalence in individuals of European descent-precisely the population with the highest frequency of rs10166942 derived allele. We thus hypothesize that local adaptation on previously neutral standing variation may have contributed to the genetic differences that exist in the prevalence of migraine among human populations today.

HEADACHE and MIGRAINE (Continued)

Meta-analysis: Second generation antidepressants and headache.

Telang S[1], Walton C[2], Olten B[1], Bloch MH[3].

J Affect Disord. **2018 Apr 9**;236:60-68. doi: 10.1016/j.jad.2018.04.047. PMID: 29715610. [Epub ahead of print]

BACKGROUND: To assess the risk of headache associated with commonly prescribed antidepressant medications and to examine the impact of medication class, pharmacodynamics and dosage on risk of headache.

METHODS: We searched PubMed to identify all randomized, double-blind, placebo-controlled trials examining the efficacy of second generation antidepressant medications in the treatment of adults with depression, anxiety or obsessive-compulsive disorders. We used a fixed-effect meta-analysis to examine the pooled risk ratio of headache reported as a side-effect in adults treated with second generation antidepressants compared to placebo. We used stratified subgroup analysis and meta-regression to examine the effects of medication type, class, dosage, indication, and receptor affinity profile on the measured risk of headache.

RESULTS: SSRIs were associated with a significantly increased risk of headache (RR = 1.06, 95%CI = 1.00-1.13, z = 2.0, p = 0.045) when compared to placebo. There was no significant difference (test for subgroup differences χ^2 = 2.2, df = 1, p = 0.14) in the risk of headache between SSRIs and SNRIs (RR = 0.97, 95%CI = 0.88-1.06, p = 0.63). There was no significant difference in the relative risk of headache with second generation antidepressants based on diagnostic indication, pharmacological properties and dosage of medications. The only antidepressants that were found to be significantly associated with increased risk of headache compared to placebo were bupropion (RR = 1.22, 95%CI = 1.06-1.41, z = 2.73, p = 0.006) and escitalopram (RR = 1.18, 95%CI = 1.01-1.37, z = 2.11, p = 0.04).

LIMITATIONS: The small number of studies that examined side effects within fixed-dose trials may have limited the power to examine the association between medication dosing and risk of headache. Additionally, reporting bias could potentially occur non-randomly across agents and therefore effect meta-analysis results.

CONCLUSIONS: Headaches reported after the initiation of second generation antidepressant medications are more likely to be coincidental than a treatment-emergent side effect of these medications.

CHRONIC PAIN

EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis.

Geenen R[1], Overman CL[1], Christensen R[2,3], Åsenlöf P[4], Capela S[5,6], Huisinga KL[7], Husebø MEP[8], Köke AJA[9], Paskins Z[10,11], Pitsillidou IA[12], Savel C[13], Austin J[1], Hassett AL[14], Severijns G[15], Stoffer-Marx M[16,17], Vlaeyen JWS[18,19], Fernández-de-Las-Peñas C[20], Ryan SJ[11], Bergman S[21].

Ann Rheum Dis. **2018 May 3**. pii: annrheumdis-2017-212662. PMID: 29724726. doi: 10.1136/annrheumdis-2017-212662. [Epub ahead of print]

Pain is the predominant symptom for people with inflammatory arthritis (IA) and osteoarthritis (OA) mandating the development of evidence-based recommendations for the health professional's approach to pain management. A multidisciplinary task force including professionals and patient representatives conducted a systematic literature review of systematic reviews to evaluate evidence regarding effects on pain of multiple treatment modalities. Overarching principles and recommendations regarding assessment and pain treatment were specified on the basis of reviewed evidence and expert opinion. From 2914 review studies initially identified, 186 met inclusion criteria. The task force emphasised the importance for the health professional to adopt a patient-centred framework within a biopsychosocial perspective, to have sufficient knowledge of IA and OA pathogenesis, and to be able to differentiate localised and generalised pain. Treatment is guided by scientific evidence and the assessment of patient needs, preferences and priorities; pain characteristics; previous and ongoing pain treatments; inflammation and joint damage; and psychological and other pain-related factors. Pain treatment options typically include education complemented by physical activity and exercise, orthotics, psychological and social interventions, sleep hygiene education, weight management, pharmacological and joint-specific treatment options, or interdisciplinary pain management. Effects on pain were most uniformly positive for physical activity and exercise interventions, and for psychological interventions. Effects on pain for educational interventions, orthotics, weight management and multidisciplinary treatment were shown for particular disease groups. Underpinned by available systematic reviews and meta-analyses, these recommendations enable health professionals to provide knowledgeable pain-management support for people with IA and OA.

CHRONIC PAIN (Continued)

Altered brain structure and function associated with sensory and affective components of classic trigeminal neuralgia.

Wang Y[1], Cao DY, Remeniuk B, Krimmel S, Seminowicz DA, Zhang M.

Pain. **2017 Aug**;158(8):1561-1570. doi: 10.1097/j.pain.0000000000000951. PMID: 28520647.

Classic trigeminal neuralgia (CTN) is a chronic neuropathic pain state characterized by intense, piercing spasms of the orofacial region, and may be attributable to abnormal pain processing in the central nervous system. Our study investigated neuronal alterations using voxel-based morphometry (VBM), diffuse tensor imaging (DTI), and resting-state functional connectivity in 38 patients with CTN and 38 matched healthy controls. For voxel-based morphometry analyses, patients with CTN displayed gray matter volume (GMV) reductions in the anterior-cingulate cortex (ACC) and mid-cingulate cortex, insula, secondary somatosensory cortex (S2), primary motor cortex (M1), premotor area, and several regions in the temporal lobe. For DTI analysis, patients compared with controls had increased mean diffusivity (MD) and decreased fractional anisotropy (FA) in the corpus callosum and the bilateral corona radiata, and increased mean diffusivity with no fractional anisotropy changes across the bilateral superior longitudinal fasciculus, the internal and external capsule, the thalamus and brainstem. Additionally, patients with CTN had enhanced functional connectivity between the right insula/S2 and ACC, medial prefrontal cortex, posterior cingulate cortex, and bilateral dorsolateral prefrontal cortex. Furthermore, gray matter volume of left inferior temporal gyrus negatively correlated with current pain intensity and disease duration in patients, and connectivity of the right insula/S2-ACC was negatively correlated with pain intensity, depression, and anxiety ratings. This study provides multiple lines of evidence supporting aberrant structural and functional patterns that are observed in patients with CTN, which may help us better understand the pathophysiology of CTN and facilitate the development of new therapies for this disease.

Genetic Factors Explain the Association Between Pain Catastrophizing and Chronic Widespread Pain.

Ogata S[1], Williams F[2], Burri A[3].

J Pain. **2017 Sep**;18(9):1111-1116. doi: 10.1016/j.jpain.2017.04.010. PMID: 28506778. Epub 2017 May 12.

This study aimed to clarify whether there are shared genetic and/or environmental factors explaining the strong link between pain catastrophizing (PC) and chronic widespread pain (CWP). Data were available for N = 1,109 female twins from TwinsUK. Information on self-reported CWP and PC was subject to variance component twin analysis. Heritabilities were 40% for PC and 77% for CWP. The genetic correlation between PC and CWP was .40%, whereas no evidence of an environmental correlation could be detected (.0). According to the best-fitting additive genetic, non-shared environmental (AE) Cholesky model, an additive genetic factor loading on PC as well as CWP, as well as an additive genetic factor loading on CWP alone was found. In terms of environmental influences, 2 individual environmental factors could be identified, loading separately on PC and CWP. Overall, the results add to the knowledge on the nature of CWP and the basis of its close relationship with PC by suggesting a shared genetic etiological structure. The findings highlight a potential avenue for future research and may provide useful insight for the clinical management of pain and pain coping.

PERSPECTIVE: Results suggest a shared genetic etiological structure between CWP and PC with no shared influence of environmental factors. Clinicians should be aware of this biological link within the context of clinical management of pain and pain coping.

CHRONIC PAIN (Continued)

Efficacy and Safety of Analgesic Treatment for Depression in People with Advanced Dementia: Randomised, Multicentre, Double-Blind, Placebo-Controlled Trial (DEP.PAIN.DEM).

Erdal A[1], Flo E[2], Aarsland D[3], Ballard C[4], Slettebo DD[5], Husebo BS[5,6].

Drugs Aging. **2018 May 3**. doi: 10.1007/s40266-018-0546-2. PMID: 29725986. [Epub ahead of print]

BACKGROUND: Chronic pain and depression often co-occur, and pain may exacerbate depression in people with dementia.

OBJECTIVE: The objective of this study was to assess the efficacy and safety of analgesic treatment for depression in nursing home patients with advanced dementia and clinically significant depressive symptoms.

METHODS: We conducted a multicentre, parallel-group, double-blind, placebo-controlled trial in 47 nursing homes, including 162 nursing home patients aged ≥ 60 years with dementia (Mini-Mental State Examination ≤ 20) and depression (Cornell Scale for Depression in Dementia ≥ 8). Patients were randomised to receive active analgesic treatment (paracetamol or buprenorphine transdermal system) or identical placebo for 13 weeks. The main outcome measure was the change in depression (Cornell Scale for Depression in Dementia) from baseline to 13 weeks, assessed using linear mixed models with fixed effects for time, intervention and their interaction in the models. Secondary outcomes were to assess whether any change in depression was secondary to change in pain (Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale) and adverse events.

RESULTS: The mean depression change was - 0.66 (95% confidence interval - 2.27 to 0.94) in the active group (n = 80) and - 3.30 (- 4.68 to -1.92) in the placebo group (n = 82). The estimated treatment effect was 2.64 (0.55-4.72, p = 0.013), indicating that analgesic treatment had no effect on depressive symptoms from baseline to 13 weeks while placebo appeared to ameliorate depressive symptoms. There was no significant reduction in pain in the active treatment group (paracetamol and buprenorphine combined) vs. placebo; however, a subgroup analysis demonstrated a significant reduction in pain for paracetamol vs. placebo [by - 1.11 (- 2.16 to - 0.06, p = 0.037)] from week 6 to 13 without a change in depression. Buprenorphine did not have significant effects on depression [3.04 (- 0.11 to 6.19), p = 0.059] or pain [0.47 (- 0.77 to 1.71), p = 0.456] from 0 to 13 weeks. Thirty-five patients were withdrawn from the study because of adverse reactions, deterioration or death: 25 (31.3%) during active treatment [23 (52.3%) who received buprenorphine], and ten (12.2%) in the placebo group. The most frequently occurring adverse events were psychiatric (17 adverse reactions) and neurological (14 adverse reactions).

CONCLUSION: Analgesic treatment did not reduce depression while placebo appeared to improve depressive symptoms significantly by comparison, possibly owing to the adverse effects of active buprenorphine. The risk of adverse events warrants caution when prescribing buprenorphine for people with advanced dementia.

TRIAL REGISTRATION: ClinicalTrials.gov **NCT02267057** (registered 7 July, 2014) and Norwegian Medicines Agency EudraCT 2013-002226-23.

OTHER RESEARCH OF INTEREST

Targeting the gut microbiome to treat the osteoarthritis of obesity.

Schott EM[1,2], Farnsworth CW[1,2], Grier A[3], Lillis JA[3], Soniwala S[1,4], Dadourian GH[5], Bell RD[1,2], Doolittle ML[1,2], Villani DA[1,2], Awad H[1,5], Ketz JP[1,6], Kamal F[1,6], Ackert-Bicknell C[1,6], Ashton JM[3], Gill SR[7], Mooney RA[1,2], Zuscik MJ[1,6].

JCI Insight. **2018 Apr 19**;3(8). pii: 95997. doi: 10.1172/jci.insight.95997. PMID: 29669931. [Epub ahead of print]

Obesity is a risk factor for osteoarthritis (OA), the greatest cause of disability in the US. The impact of obesity on OA is driven by systemic inflammation, and increased systemic inflammation is now understood to be caused by gut microbiome dysbiosis. Oligofructose, a nondigestible prebiotic fiber, can restore a lean gut microbial community profile in the context of obesity, suggesting a potentially novel approach to treat the OA of obesity. Here, we report that - compared with the lean murine gut - obesity is associated with loss of beneficial Bifidobacteria, while key proinflammatory species gain in abundance. A downstream systemic inflammatory signature culminates with macrophage migration to the synovium and accelerated knee OA. Oligofructose supplementation restores the lean gut microbiome in obese mice, in part, by supporting key commensal microflora, particularly Bifidobacterium pseudolongum. This is associated with reduced inflammation in the colon, circulation, and knee and protection from OA. This observation of a gut microbiome-OA connection sets the stage for discovery of potentially new OA therapeutics involving strategic manipulation of specific microbial species inhabiting the intestinal space.

OTHER RESEARCH OF INTEREST (Continued)

Comparing Quality of Care in Veterans Affairs and Non-Veterans Affairs Settings.

Anhang Price R[1], Sloss EM[2], Cefalu M[3], Farmer CM[4], Hussey PS[5].

J Gen Intern Med. **2018 Apr 25**. doi: 10.1007/s11606-018-4433-7. PMID: 29696561. [Epub ahead of print]

BACKGROUND: Congress, veterans' groups, and the press have expressed concerns that access to care and quality of care in Department of Veterans Affairs (VA) settings are inferior to access and quality in non-VA settings.

OBJECTIVE: To assess quality of outpatient and inpatient care in VA at the national level and facility level and to compare performance between VA and non-VA settings using recent performance measure data.

MAIN MEASURES: We assessed Patient Safety Indicators (PSIs), 30-day risk-standardized mortality and readmission measures, and ORYX measures for inpatient safety and effectiveness; Healthcare Effectiveness Data and Information Set (HEDIS®) measures for outpatient effectiveness; and Consumer Assessment of Healthcare Providers and Systems Hospital Survey (HCAHPS) and Survey of Healthcare Experiences of Patients (SHEP) survey measures for inpatient patient-centeredness. For inpatient care, we used propensity score matching to identify a subset of non-VA hospitals that were comparable to VA hospitals.

KEY RESULTS: VA hospitals performed on average the same as or significantly better than non-VA hospitals on all six measures of inpatient safety, all three inpatient mortality measures, and 12 inpatient effectiveness measures, but significantly worse than non-VA hospitals on three readmission measures and two effectiveness measures. The performance of VA facilities was significantly better than commercial HMOs and Medicaid HMOs for all 16 outpatient effectiveness measures and for Medicare HMOs, it was significantly better for 14 measures and did not differ for two measures. High variation across VA facilities in the performance of some quality measures was observed, although variation was even greater among non-VA facilities.

CONCLUSIONS: The VA system performed similarly or better than the non-VA system on most of the nationally recognized measures of inpatient and outpatient care quality, but high variation across VA facilities indicates a need for targeted quality improvement.

Neuropsychological Profile of Lifetime Traumatic Brain Injury in Older Veterans.

Kaup AR[1], Peltz C[2], Kenney K[3], Kramer JH[4], Diaz-Arrastia R[3], Yaffe K[5].

J Int Neuropsychol Soc. 2017 Jan;23(1):56-64. doi: 10.1017/S1355617716000849. PMCID: PMC5243167. PMID: 27697088. Epub 2016 Oct 4.

OBJECTIVES: The aim of this study was to characterize the neuropsychological profile of lifetime traumatic brain injury (TBI) in older Veterans.

METHODS: Participants were 169 older Veterans [mean age=79.1 years (range, 51-97 years), 89% male, 92% Caucasian], 88 with lifetime TBI and 81 without TBI, living in Veterans' retirement homes in independent residence. TBI history was ascertained with the Ohio State TBI Identification Method structured interview. Cognition was assessed with neuropsychological tests: Raw scores were converted to Z-scores compared to age-corrected normative data and combined into five domain composite Z-scores (attention/working memory, learning/memory, language, processing speed, executive functioning). We investigated the association between TBI and performance in each cognitive domain in linear mixed effects models, with and without adjustment for demographics, medical comorbidities, and psychiatric variables.

RESULTS: Compared to those without TBI, older Veterans with TBI had greater deficits in processing speed (estimate=-.52; p=.01; f 2=.08 in fully adjusted model) and executive functioning (estimate=-.41; p=.02; f 2=.06 in fully adjusted model) but performed similarly in the attention/working memory, learning/memory, and language domains (all p>.05). TBI-associated deficits were most prominent among individuals with multiple mild TBIs and those with any moderate-to-severe TBI, but were not clearly present among those with single mild TBI.

CONCLUSIONS: The neuropsychological profile of lifetime TBI in older Veterans is characterized by slowed processing speed and executive dysfunction, especially among those with greater injury burden. This pattern may reflect long-standing deficits or a TBI-associated cognitive decline process distinct from Alzheimer's disease. (JINS, 2017, 23, 56-64).

OTHER RESEARCH OF INTEREST (Continued)

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial.

Blumberger DM[1], Vila-Rodriguez F[2], Thorpe KE[3], Feffer K[4], Noda Y[5], Giacobbe P[6], Knyahnytska Y[7], Kennedy SH[8], Lam RW[9], Daskalakis ZJ[10], Downar J[11].

Lancet. **2018 Apr 28**;391(10131):1683-1692. doi: 10.1016/S0140-6736(18)30295-2. PMID: 29726344. Epub 2018 Apr 26.

BACKGROUND: Treatment-resistant major depressive disorder is common; repetitive transcranial magnetic stimulation (rTMS) by use of high-frequency (10 Hz) left-side dorsolateral prefrontal cortex stimulation is an evidence-based treatment for this disorder. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that can be delivered in 3 min, versus 37·5 min for a standard 10 Hz treatment session. We aimed to establish the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in adults with treatment-resistant depression.

METHODS: In this randomised, multicentre, non-inferiority clinical trial, we recruited patients who were referred to specialty neurostimulation centres based at three Canadian university hospitals (Centre for Addiction and Mental Health and Toronto Western Hospital, Toronto, ON, and University of British Columbia Hospital, Vancouver, BC). Participants were aged 18-65 years, were diagnosed with a current treatment-resistant major depressive episode or could not tolerate at least two antidepressants in the current episode, were receiving stable antidepressant medication doses for at least 4 weeks before baseline, and had an HRSD-17 score of at least 18. Participants were randomly allocated (1:1) to treatment groups (10 Hz rTMS or iTBS) by use of a random permuted block method, with stratification by site and number of adequate trials in which the antidepressants were unsuccessful. Treatment was delivered open-label but investigators and outcome assessors were masked to treatment groups. Participants were treated with 10 Hz rTMS or iTBS to the left dorsolateral prefrontal cortex, administered on 5 days a week for 4-6 weeks. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score, with a non-inferiority margin of 2·25 points. For the primary outcome measure, we did a per-protocol analysis of all participants who were randomly allocated to groups and who attained the primary completion point of 4 weeks. This trial is registered with ClinicalTrials.gov, number NCT01887782.

FINDINGS: Between Sept 3, 2013, and Oct 3, 2016, we randomly allocated 205 participants to receive 10 Hz rTMS and 209 participants to receive iTBS. 192 (94%) participants in the 10 Hz rTMS group and 193 (92%) in the iTBS group were assessed for the primary outcome after 4-6 weeks of treatment. HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group (adjusted difference 0·01, lower 95% CI -1·16; p=0·0011), which indicated non-inferiority of iTBS. Self-rated intensity of pain associated with treatment was greater in the iTBS group than in the 10 Hz rTMS group (mean score on verbal analogue scale 3·8 [SD 2·0] vs 3·4 [2·0] out of 10; p=0·011). Dropout rates did not differ between groups (10 Hz rTMS: 13 [6%] of 205 participants; iTBS: 16 [8%] of 209 participants); p=0·6004). The most common treatment-related adverse event was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208).

INTERPRETATION: In patients with treatment-resistant depression, iTBS was non-inferior to 10 Hz rTMS for the treatment of depression. Both treatments had low numbers of dropouts and similar side-effects, safety, and tolerability profiles. By use of iTBS, the number of patients treated per day with current rTMS devices can be increased several times without compromising clinical effectiveness.

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