GULF WAR ILLNESS

Prevalence of Chronic Multisymptom Illness/Gulf War Illness Over Time Among Millennium Cohort Participants, 2001-2016.

Porter B[1], Long K, Rull RP, Dursa EK; Millennium Cohort Study Team.

J Occup Environ Med. **2019 Oct 15**. doi: 10.1097/JOM.0000000000001716. PMID: 31626064. [Epub ahead of print]

OBJECTIVE: Chronic multisymptom illness/Gulf War illness (CMI/GWI) is the defining illness of the 1990-1991 Gulf War. However, few studies have examined changes over time in CMI/GWI prevalence.

METHODS: Prevalence of CMI/GWI over time was compared between three groups of military personnel (9,110 Gulf War veterans, 36,019 era personnel, 31,446 non-era personnel) enrolled in the Millennium Cohort Study. Post hoc analyses were conducted among participants with no reported mental and physical health conditions (N=30,093).

RESULTS: CMI/GWI prevalence increased substantially over the study period among all groups. Gulf War veterans had the highest prevalence of CMI/GWI across the study period. This finding persisted after excluding participants with mental and physical health conditions.

CONCLUSIONS: Gulf War veterans' increased risk of CMI/GWI persisted across the study period, highlighting the continued importance of screening and improving treatment options among this population.

CHRONIC FATIGUE SYNDROME

Internet-Based Cognitive Behavioral Therapy for Chronic Fatigue Syndrome Integrated in Routine Clinical Care: Implementation Study.

Worm-Smeitink M[1,2,3], van Dam A[4,5], van Es S[6], van der Vaart R[7], Evers A[7,8], Wensing M[9,10], Knoop H[1,11].

J Med Internet Res. **2019 Oct 10**;21(9):e14037. doi: 10.2196/14037. PMID: 31603428.

BACKGROUND: In a clinical trial, internet-based cognitive behavioral therapy (I-CBT) embedded in stepped care was established as noninferior to face-to-face cognitive behavioral therapy (CBT) for chronic fatigue syndrome (CFS). However, treatment effects observed in clinical trials may not necessarily be retained after implementation.

OBJECTIVE: This study aimed to investigate whether stepped care for CFS starting with I-CBT, followed by face-to-face CBT, if needed, was also effective in routine clinical care. Another objective was to explore the role of therapists' attitudes toward electronic health (eHealth) and manualized treatment on treatment outcome.

METHODS: I-CBT was implemented in five mental health care centers (MHCs) with nine treatment sites throughout the Netherlands. All patients with CFS were offered I-CBT, followed by face-to-face CBT if still severely fatigued or disabled after I-CBT. Outcomes were the Checklist Individual Strength, physical and social functioning (Short-Form 36), and limitations in daily functioning according to the Work and Social Adjustment Scale. The change scores (pre to post stepped care) were compared with a benchmark: stepped care from a randomized controlled trial (RCT) testing this treatment format. We calculated correlations of therapists' attitudes toward manualized treatment and eHealth with reduction of fatigue severity.

RESULTS: Overall, 100 CFS patients were referred to the centers. Of them, 79 started with I-CBT, 20 commenced directly with face-to-face CBT, and one did not start at all. After I-CBT, 48 patients met step-up criteria; of them, 11 stepped up to face-to-face CBT. Increase in physical functioning (score of 13.4), social functioning (20.4), and reduction of limitations (10.3) after stepped care delivered in routine clinical care fell within the benchmarks of the RCT (95% CIs: 12.8-17.6; 25.2-7.8; and 7.4-9.8, respectively). Reduction of fatigue severity in the MHCs was smaller (12.6) than in the RCT (95% CI 13.2-16.5). After I-CBT only, reduction of fatigue severity (13.2) fell within the benchmark of I-CBT alone (95% CI 11.1-14.2). Twenty therapists treated between one and 18 patients. Therapists were divided into two groups: one with the largest median reduction of fatigue and one with the smallest. Patients treated by the first group had a significantly larger reduction of fatigue severity (15.7 vs 9.0; t=2.42; P=.02). There were no (statistically significant) correlations between therapists' attitudes and reduction in fatigue.

CONCLUSIONS: This study is one of the first to evaluate stepped care with I-CBT as a first step in routine clinical care. Although fatigue severity and disabilities were reduced, reduction of fatigue severity appeared smaller than in the clinical trial. Further development of the treatment should aim at avoiding dropout and encouraging stepping up after I-CBT with limited results. Median reduction of fatigue severity varied largely between therapists. Further research will help understand the role of therapists' attitudes in treatment outcome.

HEADACHE and MIGRAINE

Calcitonin gene-related peptide levels in tear fluid are elevated in migraine patients compared to healthy controls.

Kamm K[1], Straube A[1], Ruscheweyh R[1].

Cephalalgia. **2019 Oct**;39(12):1535-1543. doi: 10.1177/0333102419856640. PMID: 31603037. Epub 2019 Jun 10.

BACKGROUND: Calcitonin gene-related peptide (CGRP) released from trigeminal nerve fibres indicates trigeminal activation and has a key role in migraine pathophysiology. The trigeminal nerve directly innervates the eye. Therefore, in this study, we compared Calcitonin gene-related peptide in tear fluid of migraine patients and healthy controls.

METHODS: Calcitonin gene-related peptide concentrations in tear fluid and plasma of 48 episodic and 45 chronic migraine patients and 48 controls were assessed using ELISA.

RESULTS: Calcitonin gene-related peptide levels in tear fluid (0.94 ± 1.11 ng/ml) were ~140 times higher than plasma concentrations (6.81 ± 4.12 pg/ml). Tear fluid CGRP concentrations were elevated in interictal migraine patients (1.10 ± 1.27 ng/ml, n = 49) compared to controls (0.75 ± 0.80 ng/ml, $p = 0.022$). There was no difference in tear fluid CGRP levels between interictal episodic and chronic migraine patients (episodic: 1.09 ± 1.47 ng/ml, n = 30 and chronic: 1.10 ± 0.89 ng/ml, n = 19) and no correlation of tear fluid CGRP levels with headache frequency in interictal patients (rho = 0.062, $p = 0.674$). Unmedicated ictal migraine patients had even more elevated tear fluid CGRP levels than interictal migraine patients (1.92 ± 1.84 ng/ml, n = 13, $p = 0.102$), while medicated ictal migraine patients had lower levels (0.56 ± 0.47 ng/ml, n = 25, $p = 0.011$ compared to interictal patients), which were undistinguishable from controls ($p = 0.609$). In contrast to tear fluid, no significant group differences were found in plasma CGRP levels.

CONCLUSION: To the best of our knowledge, this study shows, for the first time, increased CGRP tear fluid levels in migraine patients compared to healthy subjects. Detection of calcitonin gene-related peptide in tear fluid is non-invasive, and likely allows a more direct access to CGRP released from the trigeminal nerve than plasma sampling.

Positive Response to Galcanezumab Following Treatment Failure to OnabotulinumtoxinA in Patients With Migraine: Post hoc Analyses of 3 Randomized Double-Blind Studies.

Ailani J[1], Pearlman E[2], Zhang Q[3], Nagy AJ[4], Schuh K[2], Aurora SK[3].

Eur J Neurol. **2019 Oct 8**. doi: 10.1111/ene.14102. PMID: 31595600. [Epub ahead of print]

BACKGROUND AND PURPOSE: Humanized monoclonal antibody galcanezumab, which binds to calcitonin gene-related peptide, has shown efficacy for episodic and chronic migraine prevention. These analyses evaluated galcanezumab response for migraine headache prevention in patients who previously failed onabotulinumtoxinA ("nonresponse" or "inadequate response" or safety reasons).

METHODS: Post hoc analyses included data from 3 double-blind, placebo-controlled, Phase 3 episodic or chronic migraine studies; 2,886 patients randomly received 120mg or 240mg galcanezumab or placebo. During double-blind periods, study drug was administered subcutaneously once/month for 6 months in EVOLVE-1&2 and for 3 months in REGAIN. The 120mg groups received a 240mg loading dose at Month 1. Pooled analyses included 129 patients who failed onabotulinumtoxinA. Using mixed effect model repeat measurement, least squares mean change from baseline in number of migraine headache days (MHDs) was calculated for first 3 months of treatment.

RESULTS: For pooled analyses, significant decreases from baseline in number of MHDs were observed for 120mg (-3.91) and 240mg (-5.27) galcanezumab overall vs placebo (-0.88) across 3-month time points for patients who failed onabotulinumtoxinA. Corresponding data for patients with chronic migraine showed significant decreases: 120mg (-3.18) and 240mg (-4.26) galcanezumab vs placebo (0.16). Significant reductions in number of MHDs/month with acute medication use included: 120mg galcanezumab (-4.35) and 240mg galcanezumab (-4.55) vs placebo (-0.83). Estimates of ≥50% response during Months 1-3 were 9.4% for placebo, 41.3% for 120mg galcanezumab, and 47.5% for 240mg galcanezumab.

CONCLUSION: Galcanezumab is an option for prevention of migraine in patients who have previously failed onabotulinumtoxinA preventive therapy.

HEADACHE and MIGRAINE (Continued)

What is Needed for Evidence-Based Dietary Recommendations for Migraine: A Call to Action for Nutrition and Microbiome Research.

Slavin M[1], Li HA[1], Frankenfeld C[2], Cheskin LJ[1].

Headache. **2019 Oct**;59(9):1566-1581. doi: 10.1111/head.13658. PMID: 31603554.

BACKGROUND: The gastrointestinal symptoms of migraine attacks have invited numerous dietary hypotheses for migraine etiology through the centuries. Substantial efforts have been dedicated to identifying dietary interventions for migraine attack prevention, with limited success. Meanwhile, mounting evidence suggests that the reverse relationship may also exist - that the biological mechanisms of migraine may influence dietary intake. More likely, the truth involves some combination of both, where the disease influences food intake, and the foods eaten impact the manifestations of the disease. In addition, the gut's microbiota is increasingly suspected to influence the migraine brain via the gut-brain axis, though these hypotheses remain largely unsubstantiated.

OBJECTIVE: This paper presents an overview of the strength of existing evidence for food-based dietary interventions for migraine, noting that there is frequently evidence to suggest that a dietary risk factor for migraine exists but no evidence for how to best intervene; in fact, our intuitive assumptions on interventions are being challenged with new evidence. We then look to the future for promising avenues of research, notably the gut microbiome.

CONCLUSION: The evidence supports a call to action for high-quality dietary and microbiome research in migraine, both to substantiate hypothesized relationships and build the evidence base regarding nutrition's potential impact on migraine attack prevention and treatment.

CHRONIC PAIN

A Cross-Sectional Examination of Patients' Perspectives About Their Pain, Pain Management, and Satisfaction with Pain Treatment.

Lee S[1,2], Smith ML[1,2,3], Dahlke DV[1,4], Pardo N[5], Ory MG[1,2].

Pain Med. **2019 Oct 14**. pii: pnz244. doi: 10.1093/pm/pnz244. PMID: 31609389. [Epub ahead of print]

OBJECTIVE: Empirical studies show conflicting findings about the relationship between pain relief and patient satisfaction. To address this research gap, this study examines the differential effects of pain relief on patient satisfaction based on patients' perceptions about pain management.

METHODS: Cross-sectional survey data were collected from 178 adults with self-reported chronic noncancer pain (i.e., pain that typically lasts >12 weeks that is not due to cancer). Participants rated their satisfaction with pain care, pain relief, and perceptions about participation in their treatment decisions and confidence in their physicians. Multiple linear regression models were used to examine whether patients' perceptions moderated the effects of pain on patient satisfaction. All models were adjusted for age, education, and frequency of chronic pain. Based on the preliminary analyses, separate models were performed for participants who reported low (median or lower) and high (greater than median) pain relief.

RESULTS: On average, patients reported moderate patient satisfaction with their pain care (score of 5.54 out of 10, with a higher score indicating greater patient satisfaction). Among patients who reported low pain relief, the level of pain relief ($P < 0.001$) and confidence in their physicians ($P = 0.031$) were positively associated with satisfaction after adjusting for other covariates and control variables. Among patients who reported high pain relief, the level of pain relief ($P = 0.002$) positively predicted satisfaction after adjusting for other covariates and control variables. Patients' confidence in their physicians positively moderated the effects of pain relief on satisfaction among patients who reported low pain relief ($P = 0.006$), but not among patients who reported high pain relief ($P = 0.275$).

CONCLUSIONS: Interventions to improve patients' confidence in their physician's pain management may enhance the effects of pain relief on patient satisfaction, particularly among patients who experience low levels of pain alleviation during their pain treatment.

IRRITABLE BOWEL SYNDROME

No distinct microbiome signature of irritable bowel syndrome found in a Swedish random population.

Hugerth LW[1], Andreasson A[2,3,4], Talley NJ[5], Forsberg AM[3], Kjellström L[6], Schmidt PT[3], Agreus L[7], Engstrand L[8,9].

Gut. **2019 Oct 10**. pii: gutjnl-2019-318717. doi: 10.1136/gutjnl-2019-318717. PMID: 31601615. [Epub ahead of print]

OBJECTIVE: The ethiopathogenesis of irritable bowel syndrome (IBS) is unknown. While a link to the gut microbiome is postulated, the heterogeneity of the healthy gut makes it difficult to draw definitive conclusions. We aimed to describe the faecal and mucosa-associated microbiome (MAM) and health correlates on a community cohort of healthy and IBS individuals with no colonoscopic findings.

DESIGN: The PopCol study recruited a random sample of 3556 adults; 745 underwent colonoscopy. IBS was defined by Rome IV criteria and organic disease excluded. 16S rRNA gene sequencing was conducted on sigmoid biopsy samples from 376 representative individuals (63 IBS cases) and faecal samples from 185 individuals (32 IBS cases).

RESULTS: While sigmoid MAM was dominated by Lachnospiraceae, faeces presented a higher relative abundance of Ruminococcaceae. Microbial richness in MAM was linearly correlated to that in faeces from the same individual (R^2=0.255, p<3E-11) as was diversity (R^2=0.06, p=0.0022). MAM diversity decreased with increasing body mass index (BMI; Pearson's r=-0.1, p=0.08) and poorer self-rated health (r=-0.15, p=0.007), but no other health correlates. Faecal microbiome diversity was correlated to stool consistency (r=-0.16, p=0.043). Several taxonomic groups were correlated to age, BMI, depression and self-reported health, including *Coprococcus catus* associated with lower levels of depression (r=-0.003, p=0.00017). The degree of heterogeneity observed between IBS patients is higher than that observed between healthy individuals.

CONCLUSIONS: No distinct microbial signature was observed in IBS. Individuals presenting with low self-rated health or high BMI have lower gut microbiome richness.

Allogenic Faecal Microbiota Transfer Induces Immune-Related Gene Sets in the Colon Mucosa of Patients with Irritable Bowel Syndrome.

Holster S[1], Hooiveld GJ[2], Repsilber D[1], Vos WM[3,4], Brummer RJ[1], König J[5].

Biomolecules. **2019 Oct 8**;9(10). pii: E586. doi: 10.3390/biom9100586. PMCID: PMC6843426. PMID: 31597320.

Faecal microbiota transfer (FMT) consists of the introduction of new microbial communities into the intestine of a patient, with the aim of restoring a disturbed gut microbiota. Even though it is used as a potential treatment for various diseases, it is unknown how the host mucosa responds to FMT. This study aims to investigate the colonic mucosa gene expression response to allogenic (from a donor) or autologous (own) FMT in patients with irritable bowel syndrome (IBS). In a recently conducted randomised, double-blinded, controlled clinical study, 17 IBS patients were treated with FMT by colonoscopy. RNA was isolated from colonic biopsies collected by sigmoidoscopy at baseline, as well as two weeks and eight weeks after FMT. In patients treated with allogenic FMT, predominantly immune response-related gene sets were induced, with the strongest response two weeks after the FMT. In patients treated with autologous FMT, predominantly metabolism-related gene sets were affected. Furthermore, several microbiota genera showed correlations with immune-related gene sets, with different correlations found after allogenic compared to autologous FMT. This study shows that the microbe-host response is influenced by FMT on the mucosal gene expression level, and that there are clear differences in response to allogenic compared to autologous FMT.

IRRITABLE BOWEL SYNDROME (Continued)

Visceral pain from colon and rectum: the mechanotransduction and biomechanics.

Feng B[1], Guo T[2].

J Neural Transm (Vienna). **2019 Oct 9**. doi: 10.1007/s00702-019-02088-8. PMID: 31598778. [Epub ahead of print]

Visceral pain is the cardinal symptom of functional gastrointestinal (GI) disorders such as the irritable bowel syndrome (IBS) and the leading cause of patients' visit to gastroenterologists. IBS-related visceral pain usually arises from the distal colon and rectum (colorectum), an intraluminal environment that differs greatly from environment outside the body in chemical, biological, thermal, and mechanical conditions. Accordingly, visceral pain is different from cutaneous pain in several key psychophysical characteristics, which likely underlies the unsatisfactory management of visceral pain by drugs developed for other types of pain. Colorectal visceral pain is usually elicited from mechanical distension/stretch, rather than from heating, cutting, pinching, or piercing that usually evoke pain from the skin. Thus, mechanotransduction, i.e., the encoding of colorectal mechanical stimuli by sensory afferents, is crucial to the underlying mechanisms of GI-related visceral pain. This review will focus on colorectal mechanotransduction, the process of converting colorectal mechanical stimuli into trains of action potentials by the sensory afferents to inform the central nervous system (CNS). We will summarize neurophysiological studies on afferent encoding of colorectal mechanical stimuli, highlight recent advances in our understanding of colorectal biomechanics that plays critical roles in mechanotransduction, and review studies on mechano-sensitive ion channels in colorectal afferents. This review calls for focused attention on targeting colorectal mechanotransduction as a new strategy for managing visceral pain, which can also have an added benefit of limited CNS side effects, because mechanotransduction arises from peripheral organs.

OTHER RESEARCH OF INTEREST

Experiences and Knowledge of US Department of Veterans Affairs Clinical Services, Research, and Education: Results From a National Survey of Veterans.

Tsai J[1], Mehta K, Hunt-Johnson N, Pietrzak RH.

J Public Health Manag Pract. **2019 Oct 4**. doi: 10.1097/PHH.0000000000001053. PMID: 31592984. [Epub ahead of print]

OBJECTIVE: This study examined (1) sociodemographic, health, and psychosocial characteristics associated with using the Department of Veterans Affairs (VA) health care system as a primary health care provider; (2) veterans' experience and knowledge of VA clinical services, research, and education; and (3) veteran characteristics associated with VA experience and knowledge.

DESIGN: A nationally representative survey was conducted in 2018; eligibility criteria for participation were adults aged 18 years or older, currently living in the United States, and having served on active duty in the US military.

SETTING: The survey was conducted online using large national survey panels.

PARTICIPANTS: A sample of 1002 veterans across 49 states participated.

MAIN OUTCOME MEASURES: The survey assessed experience and knowledge of majority of VA clinical services, research, and education.

RESULTS: One-quarter of the total sample reported that the VA was their primary health care provider. Among veterans who had ever used VA health care, the majority (68%) reported overall high satisfaction with VA health care but also agreed with "privatizing parts of the VA" (70%). The majority (51%-73%) of veterans reported knowledge of major VA clinical services, with the exception of comprehensive management for chronic pain (24%) and treatment of opioid use disorders (31%). One-quarter to one-half also reported knowledge of several VA research and education centers. Less than 10% of veterans reported having ever used a VA mobile app.

CONCLUSIONS: The US veterans generally reported positive experiences and good knowledge of VA services and resources. Greater awareness of available VA services for chronic pain and opioid use disorders, as well as VA mobile apps, may help promote more comprehensive care in this population.

OTHER RESEARCH OF INTEREST (Continued)

Differentiating Psychosomatic, Somatopsychic, Multisystem Illnesses, and Medical Uncertainty.

Bransfield RC[1], Friedman KJ[2].

Healthcare (Basel). **2019 Oct 8**;7(4). pii: E114. doi: 10.3390/healthcare7040114. PMID: 31597359.

There is often difficulty differentiating between psychosomatic, somatopsychic, multisystem illness, and different degrees of medical uncertainty. Uncommon, complex, and multisystem diseases are commonly misdiagnosed. Two case histories are described, and relevant terms differentiating psychosomatic, somatopsychic, and multisystem illnesses are identified, reviewed, and discussed. Adequate differentiation requires an understanding of the mind/body connection, which includes knowledge of general medicine, psychiatry, and the systems linking the body and the brain. A psychiatric diagnosis cannot be given solely based upon the absence of physical, laboratory, or pathological findings. Medically unexplained symptoms, somatoform disorder, and compensation neurosis are outdated and/or inaccurate terms. The terms subjective, nonspecific, and vague can be used inaccurately. Conversion disorders, functional disorders, psychogenic illness, factitious disorder imposed upon another (Munchausen's syndrome by proxy), somatic symptom disorder, psychogenic seizures, psychogenic pain, psychogenic fatigue, and delusional parasitosis can be over-diagnosed. Bodily distress disorder and bodily distress syndrome are scientifically unsupported and inaccurate. Many "all in your head" conditions may be related to the microbiome and the immune system. Better education concerning the interface between medicine and psychiatry and the associated diagnostic nomenclature as well as utilizing clinical judgment and thorough assessment, exercising humility, and maintaining our roots in traditional medicine will help to improve diagnostic accuracy and patient trust.

OnabotulinumtoxinA for the treatment of major depressive disorder: a phase 2 randomized, double-blind, placebo-controlled trial in adult females.

Brin MF[1,2], Durgam S[3], Lum A[1], James L[1], Liu J[1], Thase ME[4], Szegedi A[5].

Int Clin Psychopharmacol. **2019 Oct 11**. doi: 10.1097/YIC.0000000000000290. PMID: 31609787. [Epub ahead of print]

This 24-week double-blind placebo-controlled multicenter randomized phase 2 trial evaluated efficacy and safety of onabotulinumtoxinA (onabotA; BOTOX) vs. placebo for major depressive disorder (MDD) [NCT02116361]. Primary endpoint was the change in Montgomery-Åsberg Depression Rating Scale (MADRS); secondary endpoints were Clinical Global Impressions-Severity and 17-item Hamilton Depression Rating Scale at week 6. A total of 255 adult females were treated. OnabotA 30 U approached significance compared to placebo on MADRS (mixed-effect model repeated measures least-squares mean difference: -3.7; P = 0.053) and reached significance [least-squares mean differences: -3.6 to -4.2; P < 0.05 (two-sided)] at weeks 3 and 9. Secondary endpoints were also significant at several time points. At week 6, onabotA 50 U did not separate from placebo in any parameters. OnabotA was generally well-tolerated: the only treatment-emergent adverse events reported in ≥5% in either onabotA group, and more than matching placebo were headache, upper respiratory infection, and eyelid ptosis. OnabotA 30 U, administered in a standardized injection pattern in a single session, had a consistent efficacy signal across multiple depression symptom scales for 12 or more weeks. OnabotA 30 U/placebo MADRS differences of (observed ANCOVA) ≥4.0 points (up to week 15) and ≥2.0 points (weeks 18-24) agree with the 2-point change threshold considered clinically relevant in MDD. OnabotA is a local therapy and is not commonly associated with systemic effects of conventional antidepressants and may represent a novel treatment option for MDD.

OTHER RESEARCH OF INTEREST (Continued)

Extended treatment with fingolimod for relapsing multiple sclerosis: the 14-year LONGTERMS study results.

Cohen JA[1], Tenenbaum N[2], Bhatt A[3], Zhang Y[2], Kappos L[4].

Ther Adv Neurol Disord. **2019 Sep 25**;12:1756286419878324. doi: 10.1177/1756286419878324. PMCID: PMC6763939. PMID: 31598139.

Background: Multiple sclerosis (MS) is a chronic disease that may require decades of ongoing treatment. Therefore, the long-term safety and efficacy of disease-modifying therapies is an important consideration.

Methods: The LONGTERMS study evaluated the safety and efficacy of fingolimod in patients with relapsing MS (RMS) with up to 14 years of exposure. This phase IIIb, open-label extension study included patients aged ⩾ 18 years with confirmed RMS diagnosis who completed previous phase II/III/IIIb core/extension studies of fingolimod. Patients received fingolimod 0.5 mg orally once daily; safety and efficacy (clinical and magnetic resonance imaging) were the main outcomes.

Results: Of 4086 patients from the core studies who entered LONGTERMS, 3480 (85.2%) completed the study. The median age (range) was 38 (17-65) years and median fingolimod exposure was 944.5 (range 75-4777) days. Overall, 85.5% of patients experienced at least one adverse event (AE); most common AEs (⩾10%) were viral upper respiratory tract infection (17.3%), headache (13.3%), hypertension (11.0%) and lymphopenia (10.7%). Among patients with serious AEs (12.6%), basal cell carcinoma and MS relapse (0.9% each) were most frequently reported. The aggregate annualized relapse rate decreased from 0.22 (in years 0-2) to 0.17 (years 0-10); 45.5% of patients remained relapse free after 10 years. At year 10, 63.2% of patients were free from 6-month confirmed disability worsening.

Conclusion: This long-term observational study of patients treated for up to 14 years with fingolimod confirmed its established safety profile with no new safety concerns. Patients with RMS receiving fingolimod had sustained low levels of disease activity and progression.

Trial Registration: ClinicalTrials.gov identifier: NCT01201356.

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