

## GULF WAR ILLNESS

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

## CHRONIC FATIGUE SYNDROME

### [A 4-Day Mindfulness-Based Cognitive Behavioral Intervention Program for CFS/ME. An Open Study, With 1-Year Follow-Up.](#)

[Stubhaug B](#)<sup>1,2</sup>, [Lier HO](#)<sup>1</sup>, [Aßmus J](#)<sup>3</sup>, [Rongve A](#)<sup>1,2</sup>, [Kvale G](#)<sup>4,5</sup>.

Front Psychiatry. 2018 Dec 20;9:720. doi: 10.3389/fpsy.2018.00720. PMID: 30618889. eCollection 2018.

**Background:** Chronic Fatigue Syndrome/Myalgic Encephalopathy (CFS/ME) is an incapacitating illness in which single treatment interventions seem to have variable effects. Based on an earlier study we have conducted a new study with a concentrated intervention program. The aims of this study were to: (1) explore the clinical course for patients with CFS/ME who participated in a treatment program delivered during four consecutive days, and (2) evaluate their satisfaction with this program.

**Methods:** 305 patients diagnosed with CFS/ME (Oxford criteria), recruited from a clinical population referred to a specialist outpatient clinic, participated in an open uncontrolled study of the clinical course through 1 year. The study group participated in a 4-day group intervention program, comprised by education, cognitive group therapy sessions, mindfulness sessions, physical activity and writing sessions, within a context of cognitive behavioral therapy, mindfulness, acceptance and commitment model. Assessments were done by self-reports prior to the first consultation, 1 week before and 1 week after the intervention program, and at 3 months and 1 year after the intervention. SPSS 23 and R 3.3 were used for statistical analyses. The associations between case definitions and the outcome measures (Chalder Fatigue Scale (FS), Short Form 36 (SF-36) physical functioning scale) were assessed by a linear mixed effects model (LME).

**Results:** Results showed statistically significant clinical changes for 80% of the patients after the intervention, changes being sustained through 1 year after the program. For both Fatigue Scale (FS) and the SF-36 there were statistically significant effects of time from baseline to all time points with a statistically significant drop in scores, applying the linear mixed effects model. A subgroup fulfilling the inclusion criteria from the PACE study (Chalder Fatigue Scale >6/11, SF-36 Physical functioning <65/100) showed clinically significant improvement through 1 year, changes in outcome measures were statistically significant ( $p < 0.001$ ). None of the patients included in the program dropped out, and a great majority of patients expressed high satisfaction with the content, focus and amount of treatment.

**Conclusion:** Clinical changes observed from pre-treatment to 1 year follow-up could represent effects of the 4-day concentrated intervention program, and should be further explored in a controlled study.

### [Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy.](#)

[Mueller C](#)<sup>1</sup>, [Lin JC](#)<sup>1</sup>, [Sheriff S](#)<sup>2</sup>, [Maudsley AA](#)<sup>2</sup>, [Younger JW](#)<sup>3</sup>.

Brain Imaging Behav. 2019 Jan 7. doi: 10.1007/s11682-018-0029-4. PMID: 30617782. [Epub ahead of print]

Previous neuroimaging studies have detected markers of neuroinflammation in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Magnetic Resonance Spectroscopy (MRS) is suitable for measuring brain metabolites linked to inflammation, but has only been applied to discrete regions of interest in ME/CFS. We extended the MRS analysis of ME/CFS by capturing multi-voxel information across the entire brain. Additionally, we tested whether MRS-derived brain temperature is elevated in ME/CFS patients. Fifteen women with ME/CFS and 15 age- and gender-matched healthy controls completed fatigue and mood symptom questionnaires and whole-brain echo-planar spectroscopic imaging (EPSI). Choline (CHO), myo-inositol (MI), lactate (LAC), and N-acetylaspartate (NAA) were quantified in 47 regions, expressed as ratios over creatine (CR), and compared between ME/CFS patients and controls using independent-samples t-tests. Brain temperature was similarly tested between groups. Significant between-group differences were detected in several regions, most notably elevated CHO/CR in the left anterior cingulate ( $p < 0.001$ ). Metabolite ratios in seven regions were correlated with fatigue ( $p < 0.05$ ). ME/CFS patients had increased temperature in the right insula, putamen, frontal cortex, thalamus, and the cerebellum (all  $p < 0.05$ ), which was not attributable to increased body temperature or differences in cerebral perfusion. Brain temperature increases converged with elevated LAC/CR in the right insula, right thalamus, and cerebellum (all  $p < 0.05$ ). We report metabolite and temperature abnormalities in ME/CFS patients in widely distributed regions. Our findings may indicate that ME/CFS involves neuroinflammation.

## CHRONIC FATIGUE SYNDROME (Continued)

### [Hope, disappointment and perseverance: Reflections of people with Myalgic encephalomyelitis/Chronic Fatigue Syndrome \(ME/CFS\) and Multiple Sclerosis participating in biomedical research. A qualitative focus group study.](#)

[Lacerda EM](#)<sup>1</sup>, [McDermott C](#)<sup>2</sup>, [Kingdon CC](#)<sup>1</sup>, [Butterworth J](#)<sup>1</sup>, [Cliff JM](#)<sup>3</sup>, [Nacul L](#)<sup>1</sup>.

Health Expect. **2019 Jan 10**. doi: 10.1111/hex.12857. PMID: 30632248. [Epub ahead of print]

**BACKGROUND:** The Clinical Understanding and Research Excellence in ME/CFS group (CureME) at the London School of Hygiene & Tropical Medicine has supported and undertaken studies in immunology, genetics, virology, clinical medicine, epidemiology and disability. It established the UK ME/CFS Biobank (UKMEB), which stores data and samples from three groups: participants with ME/CFS, Multiple Sclerosis (MS) and healthy controls. Patient and public involvement have played a central role from its inception.

**AIM:** To explore the views of participants with ME/CFS and MS on CureME research findings, dissemination and future biomedical research priorities.

**METHOD:** Five ME/CFS and MS focus groups were conducted at two UK sites. Discussions were transcribed and analysed thematically.

**RESULTS:** A total of 28 UKMEB participants took part: 16 with ME/CFS and 12 with MS. Five themes emerged: (a) Seeking coherence: participants' reactions to initial research findings; (b) Seeking acceptance: participants explore issues of stigma and validation; (c) Seeking a diagnosis: participants explore issues around diagnosis in their lives; (d) Seeking a better future: participants' ideas on future research; and (e) Seeking to share understanding: participants' views on dissemination. Focus groups perceived progress in ME/CFS and MS research in terms of "putting together a jigsaw" of evidence through perseverance and collaboration.

**CONCLUSION:** This study provides insight into the emotional, social and practical importance of research to people with MS and ME/CFS, suggesting a range of research topics for the future. Findings should inform biomedical research directions in ME/CFS and MS, adding patients' voices to a call for a more collaborative research culture.

## HEADACHE and MIGRAINE

### [Sex Differences in Prevalence, Symptoms, Impact, and Psychiatric Comorbidities in Migraine and Probable Migraine: A Population-Based Study.](#)

[Song TJ](#)<sup>1</sup>, [Cho SJ](#)<sup>2</sup>, [Kim WJ](#)<sup>3</sup>, [Yang KI](#)<sup>4</sup>, [Yun CH](#)<sup>5</sup>, [Chu MK](#)<sup>6</sup>.

Headache. **2019 Jan 9**. doi: 10.1111/head.13470. PMID: 30623976. [Epub ahead of print]

**OBJECTIVE:** This study was conducted to investigate sex differences in the prevalence and clinical presentation of migraine and probable migraine in a general population-based sample.

**BACKGROUND:** While there is research on sex differences in clinical characteristics and their impact on migraine headache, only few studies have investigated sex differences in probable migraine in population-based settings. Moreover, compared with Western countries, the prevalence of probable migraine in Asia is relatively high. This cross-sectional study was designed to investigate sex differences in the prevalence and clinical presentation of migraine and probable migraine in a general population-based sample.

**METHODS:** We used the data of the Korean Headache-Sleep Study, which is a nationwide survey on headache and sleep.

**RESULTS:** We interviewed 7430 people, and 3114 of them agreed to participate in our study (rejection rate, 58.1%). Among these people, 419 withdrew their participation during the interview. Ultimately, 2695 people completed our survey (cooperation rate, 36.3%). The prevalence of overall migraine and probable migraine was 350/1350 (25.9%) for women and 172/1345 (12.8%) for men ( $P < .001$ , respectively). The prevalence of migraine (107/1350 [7.9%] vs 36/1345 [2.7%],  $P < .001$ ) and probable migraine (243/1350 [18.0%] vs 136/1345 [10.1%],  $P < .001$ ) was significantly higher among women than among men. Headache frequency per month (median [interquartile range]) (1.0 [0.3-3.0] vs 0.8 [0.3-2.0],  $P = .037$ ), the visual analog scale score for headache intensity (5.0 [4.0-7.0] vs 5.0 [3.0-6.0],  $P = .019$ ), and the impact of headache {Headache Impact Test-6 score (47.0 [42.0-54.0] vs 44.0 [42.0-51.8],  $P = .013$ )} were significantly higher among women with probable migraine than men. Headache frequency per month (2.0 [0.4-4.0] vs 1.0 [0.3-2.0],  $P = .073$ ), headache intensity (6.0 [5.0-8.0] vs 6.0 [4.2-7.0],  $P = .281$ ), and the impact of headache (55.0 [48.0-61.0] vs 49.0 [46.3-60.8],  $P = .225$ ) were not significantly different between women and men with migraine. Other comorbidities or associated symptoms, such as anxiety and depression, were not significantly different between women and men with migraine and probable migraine, except for nausea in probable migraine.

**CONCLUSION:** Women experience more severe symptoms and a higher impact of headache than men among participants with probable migraine. Our findings suggest that women with PM need a more intensive evaluation and treatment than men with PM.

## HEADACHE and MIGRAINE (Continued)

### [Effectiveness of Oxygen and Other Acute Treatments for Cluster Headache: Results From the Cluster Headache Questionnaire, an International Survey.](#)

[Pearson SM](#)<sup>1</sup>, [Burish MJ](#)<sup>2</sup>, [Shapiro RE](#)<sup>3</sup>, [Yan Y](#)<sup>2</sup>, [Schor LI](#)<sup>1</sup>.

Headache. **2019 Jan 11**. doi: 10.1111/head.13473. PMID: 30632614. [Epub ahead of print]

**OBJECTIVE:** To assess the effectiveness and adverse effects of acute cluster headache medications in a large international sample, including recommended treatments such as oxygen, commonly used medications such as opioids, and emerging medications such as intranasal ketamine. Particular focus is paid to a large subset of respondents 65 years of age or older.

**BACKGROUND:** Large international surveys of cluster headache are rare, as are examinations of treatments and side effects in older cluster headache patients. This article presents data from the Cluster Headache Questionnaire, with respondents from over 50 countries and with the vast majority from the United States, the United Kingdom, and Canada.

**METHODS:** This internet-based survey included questions on cluster headache diagnostic criteria, which were used as part of the inclusion/exclusion criteria for the study, as well as effectiveness of medications, physical and medical complications, psychological and emotional complications, mood scores, and difficulty obtaining medications. The diagnostic questions were also used to create a separate group of respondents with probable cluster headache. Limitations to the methods include the use of nonvalidated questions, the lack of a formal clinical diagnosis of cluster headache, and the grouping of some medications (eg, all triptans as opposed to sumatriptan subcutaneous alone).

**RESULTS:** A total of 3251 subjects participated in the questionnaire, and 2193 respondents met criteria for this study (1604 cluster headache and 589 probable cluster headache). Of the respondents with cluster headache, 68.8% (1104/1604) were male and 78.0% (1245/1596) had episodic cluster headache. Over half of respondents reported complete or very effective treatment for triptans (54%, 639/1139) and oxygen (54%, 582/1082). Between 14 and 25% of respondents reported complete or very effective treatment for ergot derivatives (dihydroergotamine 25%, 42/170; cafergot/ergotamine 17%, 50/303), caffeine and energy drinks (17%, 7/41), and intranasal ketamine (14%, 5/37). Less than 10% reported complete or very effective treatment for opioids (6%, 30/541), intranasal capsaicin (5%, 7/151), and intranasal lidocaine (2%, 5/241). Adverse events were especially low for oxygen (no or minimal physical and medical complications 99%, 1077/1093; no or minimal psychological and emotional complications 97%, 1065/1093), intranasal lidocaine (no or minimal physical and medical complications 97%, 248/257; no or minimal psychological and emotional complications 98%, 251/257), intranasal ketamine (no or minimal physical and medical complications 95%, 38/40; no or minimal psychological and emotional complications 98%, 39/40), intranasal capsaicin (no or minimal physical and medical complications 91%, 145/159; no or minimal psychological and emotional complications 94%, 150/159), and caffeine and energy drinks (no or minimal physical and medical complications 89%, 39/44; no or minimal psychological and emotional complications 91%, 40/44). This is in comparison to ergotamine/cafergot (no or minimal physical and medical complications 83%, 273/327; no or minimal psychological and emotional complications 89%, 290/327), dihydroergotamine (no or minimal physical and medical complications 81%, 143/176; no or minimal psychological and emotional complications 91%, 160/176), opioids (no or minimal physical and medical complications 76%, 416/549; no or minimal psychological and emotional complications 77%, 423/549), or triptans (no or minimal physical and medical complications 73%, 883/1218; no or minimal psychological and emotional complications 85%, 1032/1218). A total of 139 of 1604 cluster headache respondents (8.7%) were age 65 and older and reported similar effectiveness and adverse events to the general population. The 589 respondents with probable cluster headache reported similar medication effectiveness to respondents with a full diagnosis of cluster headache.

**CONCLUSIONS:** Oxygen is reported by survey respondents to be a highly effective treatment with few complications in cluster headache in a large international sample, including those 65 years or over. Triptans are also very effective with some side effects, and newer medications deserve additional study. Patients with probable cluster headache may respond similarly to acute medications as patients with a full diagnosis of cluster headache.

## HEADACHE and MIGRAINE (Continued)

### [Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety.](#)

[Blumenfeld AM](#)<sup>1</sup>, [Tepper SJ](#)<sup>2</sup>, [Robbins LD](#)<sup>3</sup>, [Manack Adams A](#)<sup>4</sup>, [Buse DC](#)<sup>5</sup>, [Orejudos A](#)<sup>4</sup>, [D Silberstein S](#)<sup>6</sup>.

J Neurol Neurosurg Psychiatry. 2019 Jan 10. pii: jnnp-2018-319290. doi: 10.1136/jnnp-2018-319290. PMID: 30630956. [Epub ahead of print]

**OBJECTIVE:** To assess the effects of onabotulinumtoxinA treatment for chronic migraine (CM) on comorbid symptoms of depression, anxiety, fatigue and poor sleep quality.

**METHODS:** The Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy open-Label (COMPEL) study is a multicentre, open-label, prospective study assessing the long-term safety and efficacy of onabotulinumtoxinA 155 U over nine treatments (108 weeks) in adults with CM. The Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder (GAD-7) scales were used to assess the effects of onabotulinumtoxinA on comorbid symptoms of depression and anxiety, respectively. A clinically meaningful improvement was assessed by the percentage of patients experiencing a  $\geq 1$  severity category reduction in PHQ-9 and GAD-7. The effects of onabotulinumtoxinA on associated sleep quality and fatigue were assessed using the Pittsburgh Sleep Quality Index and Fatigue Severity Scale, respectively.

**RESULTS:** OnabotulinumtoxinA treatment was associated with sustained reduction in headache days and PHQ-9 and GAD-7 scores in the analysis population ( $n=715$ ) over 108 weeks. PHQ-9 and GAD-7 scores were significantly reduced at all time points in patients with clinically significant symptoms of depression and/or anxiety at baseline. By week 108, 78.0% and 81.5% had clinically meaningful improvement in depression and anxiety symptoms, respectively. Sleep quality and symptoms of fatigue also improved; however, less is understood about clinically meaningful changes in these measures. No new safety concerns were identified.

**CONCLUSION:** In addition to reducing headache frequency, onabotulinumtoxinA treatment for CM was associated with clinically meaningful reduction in symptoms of depression and anxiety, and improved associated symptoms of poor sleep quality and fatigue.

**TRIAL REGISTRATION NUMBER:** [NCT01516892](#).

## CHRONIC PAIN

### [Scrambler therapy: what's new after 15 years? The results from 219 patients treated for chronic pain.](#)

[Ricci M](#)<sup>1</sup>, [Fabbri L](#)<sup>2</sup>, [Pirotti S](#)<sup>2</sup>, [Ruffilli N](#)<sup>2</sup>, [Foca F](#)<sup>3</sup>, [Maltoni M](#)<sup>1,2</sup>.

Medicine (Baltimore). 2019 Jan;98(2):e13895. doi: 10.1097/MD.00000000000013895. PMID: 30633163.

Chronic pain is often difficult to treat, requiring a comprehensive multidisciplinary therapeutic intervention and a high level of management expertise. This is particularly true for patients who are unresponsive to standard treatments for chronic pain, for which Scrambler Therapy (ST) is indicated. The aim of the present study was to evaluate the impact of ST on patient-reported moderate to severe chronic pain. This was a prospective trial on 219 patients affected by chronic pain from April 2010 to March 2016. The study consisted of 2 consecutive weeks of treatment with ST (one 30-min daily session, 5 days a week) (T0, T1, T2) and a 2-week follow-up (T3, T4). Patients were asked to describe the pain using the Numeric Rating Scale (NRS) immediately prior to and after the treatment. Two hundred nineteen patients were treated for chronic pain of different nature with mean values of 6.44 ( $\pm 2.11$ ) at T0, 3.22 ( $\pm 2.20$ ) at T2, and 3.19 ( $\pm 2.34$ ) at T4. A reduction in the symptomatology from T0 to T2 was maintained throughout T4 ( $P$  value  $< .0001$ ). Of the 219 patients treated with ST, 83 (37.9%) had cancer pain and 136 (62.1%) had non-cancer pain. No adverse events were reported. Future research should focus on individual response, retreatment, and maintenance therapy. The data showed a statistically significant impact of ST, which was maintained during follow-up, on patients suffering from chronic pain of different nature.

## CHRONIC PAIN (Continued)

### [Exercise-induced hypoalgesia: A meta-analysis of exercise dosing for the treatment of chronic pain.](#)

[Polaski AM](#)<sup>1,2</sup>, [Phelps AL](#)<sup>2,3</sup>, [Kostek MC](#)<sup>2,4</sup>, [Szucs KA](#)<sup>2,5</sup>, [Kolber BJ](#)<sup>1,2</sup>.

PLoS One. **2019 Jan 9**;14(1):e0210418. doi: 10.1371/journal.pone.0210418. PMID: 30625201. eCollection 2019.

**OBJECTIVE:** Increasing evidence purports exercise as a first-line therapeutic for the treatment of nearly all forms of chronic pain. However, knowledge of efficacious dosing respective to treatment modality and pain condition is virtually absent in the literature. The purpose of this analysis was to calculate the extent to which exercise treatment shows dose-dependent effects similar to what is seen with pharmacological treatments.

**METHODS:** A recently published comprehensive review of exercise and physical activity for chronic pain in adults was identified in May 2017. This report reviewed different physical activity and exercise interventions and their effectiveness in reducing pain severity and found overall modest effects of exercise in the treatment of pain. We analyzed this existing data set, focusing specifically on the dose of exercise intervention in these studies. We re-analyzed data from 75 studies looking at benefits of time of exercising per week, frequency of exercise per week, duration of intervention (in weeks), and estimated intensity of exercise.

**RESULTS:** Analysis revealed a significant positive correlation with exercise duration and analgesic effect on neck pain. Multiple linear regression modeling of these data predicted that increasing the frequency of exercise sessions per week is most likely to have a positive effect on chronic pain patients.

**DISCUSSION:** Modest effects were observed with one significant correlation between duration and pain effect for neck pain. Overall, these results provide insufficient evidence to conclude the presence of a strong dose effect of exercise in pain, but our modeling data provide test predictions that can be used to design future studies to explicitly test the question of dose in specific patient populations.

## OTHER RESEARCH OF INTEREST

### [Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial.](#)

[Costello SP](#)<sup>1,2,3</sup>, [Hughes PA](#)<sup>1</sup>, [Waters O](#)<sup>4</sup>, [Bryant RV](#)<sup>1,2,3</sup>, [Vincent AD](#)<sup>5</sup>, [Blatchford P](#)<sup>6</sup>, [Katsikeros R](#)<sup>3</sup>, [Makanyanga J](#)<sup>4</sup>, [Campaniello MA](#)<sup>1</sup>, [Mavrangelos C](#)<sup>1</sup>, [Rosewarne CP](#)<sup>6</sup>, [Bickley C](#)<sup>6</sup>, [Peters C](#)<sup>2</sup>, [Schoeman MN](#)<sup>1,2</sup>, [Conlon MA](#)<sup>6</sup>, [Roberts-Thomson IC](#)<sup>1,3</sup>, [Andrews JM](#)<sup>1,2</sup>.

JAMA. **2019 Jan 15**;321(2):156-164. doi: 10.1001/jama.2018.20046. PMID: 30644982.

**Importance:** High-intensity, aerobically prepared fecal microbiota transplantation (FMT) has demonstrated efficacy in treating active ulcerative colitis (UC). FMT protocols involving anaerobic stool processing methods may enhance microbial viability and allow efficacy with a lower treatment intensity.

**Objective:** To assess the efficacy of a short duration of FMT therapy to induce remission in UC using anaerobically prepared stool.

**Design, Setting, and Participants:** A total of 73 adults with mild to moderately active UC were enrolled in a multicenter, randomized, double-blind clinical trial in 3 Australian tertiary referral centers between June 2013 and June 2016, with 12-month follow-up until June 2017.

**Interventions:** Patients were randomized to receive either anaerobically prepared pooled donor FMT (n = 38) or autologous FMT (n = 35) via colonoscopy followed by 2 enemas over 7 days. Open-label therapy was offered to autologous FMT participants at 8 weeks and they were followed up for 12 months.

**Main Outcomes and Measures:** The primary outcome was steroid-free remission of UC, defined as a total Mayo score of  $\leq 2$  with an endoscopic Mayo score of 1 or less at week 8. Total Mayo score ranges from 0 to 12 (0 = no disease and 12 = most severe disease). Steroid-free remission of UC was reassessed at 12 months. Secondary clinical outcomes included adverse events.

**Results:** Among 73 patients who were randomized (mean age, 39 years; women, 33 [45%]), 69 (95%) completed the trial. The primary outcome was achieved in 12 of the 38 participants (32%) receiving pooled donor FMT compared with 3 of the 35 (9%) receiving autologous FMT (difference, 23% [95% CI, 4%-42%]; odds ratio, 5.0 [95% CI, 1.2-20.1]; P = .03). Five of the 12 participants (42%) who achieved the primary end point at week 8 following donor FMT maintained remission at 12 months. There were 3 serious adverse events in the donor FMT group and 2 in the autologous FMT group.

**Conclusions and Relevance:** In this preliminary study of adults with mild to moderate UC, 1-week treatment with anaerobically prepared donor FMT compared with autologous FMT resulted in a higher likelihood of remission at 8 weeks. Further research is needed to assess longer-term maintenance of remission and safety.

**Trial Registration:** anzctr.org.au Identifier: ACTRN12613000236796

## OTHER RESEARCH OF INTEREST (Continued)

[Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis.](#)

[Brown JW](#)<sup>1,2,3</sup>, [Coles A](#)<sup>1</sup>, [Horakova D](#)<sup>4,5</sup>, [Havrdova E](#)<sup>4,5</sup>, [Izquierdo G](#)<sup>6</sup>, [Prat A](#)<sup>7,8</sup>, [Girard M](#)<sup>7,8</sup>, [Duquette P](#)<sup>7,8</sup>, [Trojano M](#)<sup>9</sup>, [Lugaresi A](#)<sup>10</sup>, [Bergamaschi R](#)<sup>11</sup>, [Grammond P](#)<sup>12</sup>, [Alroughani R](#)<sup>13</sup>, [Hupperts R](#)<sup>14</sup>, [McCombe P](#)<sup>15</sup>, [Van Pesch V](#)<sup>16</sup>, [Sola P](#)<sup>17</sup>, [Ferraro D](#)<sup>17</sup>, [Grand'Maison F](#)<sup>18</sup>, [Terzi M](#)<sup>19</sup>, [Lechner-Scott J](#)<sup>20,21</sup>, [Flechter S](#)<sup>22</sup>, [Slee M](#)<sup>23</sup>, [Shaygannejad V](#)<sup>24</sup>, [Pucci E](#)<sup>25</sup>, [Granella F](#)<sup>26</sup>, [Jokubaitis V](#)<sup>27,28</sup>, [Willis M](#)<sup>29</sup>, [Rice C](#)<sup>30</sup>, [Scolding N](#)<sup>30</sup>, [Wilkins A](#)<sup>30</sup>, [Pearson OR](#)<sup>31</sup>, [Ziemssen T](#)<sup>32</sup>, [Hutchinson M](#)<sup>33</sup>, [Harding K](#)<sup>34</sup>, [Jones J](#)<sup>1</sup>, [McGuigan C](#)<sup>33</sup>, [Butzkueven H](#)<sup>27,28,35</sup>, [Kalincik T](#)<sup>3,27,28</sup>, [Robertson N](#)<sup>34</sup>, [MSBase Study Group](#).

JAMA. 2019 Jan 15;321(2):175-187. doi: 10.1001/jama.2018.20588. PMID: 30644981.

**Importance:** Within 2 decades of onset, 80% of untreated patients with relapsing-remitting multiple sclerosis (MS) convert to a phase of irreversible disability accrual termed secondary progressive MS. The association between disease-modifying treatments (DMTs), and this conversion has rarely been studied and never using a validated definition.

**Objective:** To determine the association between the use, the type of, and the timing of DMTs with the risk of conversion to secondary progressive MS diagnosed with a validated definition.

**Design, Setting, and Participants:** Cohort study with prospective data from 68 neurology centers in 21 countries examining patients with relapsing-remitting MS commencing DMTs (or clinical monitoring) between 1988-2012 with minimum 4 years' follow-up.

**Exposures:** The use, type, and timing of the following DMTs: interferon beta, glatiramer acetate, fingolimod, natalizumab, or alemtuzumab. After propensity-score matching, 1555 patients were included (last follow-up, February 14, 2017).

**Main Outcome and Measure:** Conversion to objectively defined secondary progressive MS.

**Results:** Of the 1555 patients, 1123 were female (mean baseline age, 35 years [SD, 10]). Patients initially treated with glatiramer acetate or interferon beta had a lower hazard of conversion to secondary progressive MS than matched untreated patients (HR, 0.71; 95% CI, 0.61-0.81;  $P < .001$ ; 5-year absolute risk, 12% [49 of 407] vs 27% [58 of 213]; median follow-up, 7.6 years [IQR, 5.8-9.6]), as did fingolimod (HR, 0.37; 95% CI, 0.22-0.62;  $P < .001$ ; 5-year absolute risk, 7% [6 of 85] vs 32% [56 of 174]; median follow-up, 4.5 years [IQR, 4.3-5.1]); natalizumab (HR, 0.61; 95% CI, 0.43-0.86;  $P = .005$ ; 5-year absolute risk, 19% [16 of 82] vs 38% [62 of 164]; median follow-up, 4.9 years [IQR, 4.4-5.8]); and alemtuzumab (HR, 0.52; 95% CI, 0.32-0.85;  $P = .009$ ; 5-year absolute risk, 10% [4 of 44] vs 25% [23 of 92]; median follow-up, 7.4 years [IQR, 6.0-8.6]). Initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion than initial treatment with glatiramer acetate or interferon beta (HR, 0.66; 95% CI, 0.44-0.99;  $P = .046$ ); 5-year absolute risk, 7% [16 of 235] vs 12% [46 of 380]; median follow-up, 5.8 years [IQR, 4.7-8.0]). The probability of conversion was lower when glatiramer acetate or interferon beta was started within 5 years of disease onset vs later (HR, 0.77; 95% CI, 0.61-0.98;  $P = .03$ ; 5-year absolute risk, 3% [4 of 120] vs 6% [2 of 38]; median follow-up, 13.4 years [IQR, 11-18.1]). When glatiramer acetate or interferon beta were escalated to fingolimod, alemtuzumab, or natalizumab within 5 years vs later, the HR was 0.76 (95% CI, 0.66-0.88;  $P < .001$ ; 5-year absolute risk, 8% [25 of 307] vs 14% [46 of 331], median follow-up, 5.3 years [IQR, 4.6-6.1]).

**Conclusions and Relevance:** Among patients with relapsing-remitting MS, initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion to secondary progressive MS vs initial treatment with glatiramer acetate or interferon beta. These findings, considered along with these therapies' risks, may help inform decisions about DMT selection.

## OTHER RESEARCH OF INTEREST (Continued)

**Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial.**

[Burt RK<sup>1</sup>](#), [Balabanov R<sup>2</sup>](#), [Burman J<sup>3</sup>](#), [Sharrack B<sup>4</sup>](#), [Snowden JA<sup>5</sup>](#), [Oliveira MC<sup>6</sup>](#), [Fagius J<sup>3</sup>](#), [Rose J<sup>7</sup>](#), [Nelson F<sup>8</sup>](#), [Barreira AA<sup>9</sup>](#), [Carlson K<sup>10</sup>](#), [Han X<sup>1</sup>](#), [Morales D<sup>6</sup>](#), [Morgan A<sup>1</sup>](#), [Quigley K<sup>1</sup>](#), [Yaung K<sup>1</sup>](#), [Buckley R<sup>1</sup>](#), [Alldredge C<sup>1</sup>](#), [Clendenan A<sup>1</sup>](#), [Calvario MA<sup>1</sup>](#), [Henry J<sup>1</sup>](#), [Jovanovic B<sup>11</sup>](#), [Helenowski IB<sup>11</sup>](#).

JAMA. 2019 Jan 15;321(2):165-174. doi: 10.1001/jama.2018.18743.

**Importance:** Hematopoietic stem cell transplantation (HSCT) represents a potentially useful approach to slow or prevent progressive disability in relapsing-remitting multiple sclerosis (MS).

**Objective:** To compare the effect of nonmyeloablative HSCT vs disease-modifying therapy (DMT) on disease progression.

**Design, Setting, and Participants:** Between September 20, 2005, and July 7, 2016, a total of 110 patients with relapsing-remitting MS, at least 2 relapses while receiving DMT in the prior year, and an Expanded Disability Status Scale (EDSS; score range, 0-10 [10 = worst neurologic disability]) score of 2.0 to 6.0 were randomized at 4 US, European, and South American centers. Final follow-up occurred in January 2018 and database lock in February 2018.

**Interventions:** Patients were randomized to receive HSCT along with cyclophosphamide (200 mg/kg) and antithymocyte globulin (6 mg/kg) (n = 55) or DMT of higher efficacy or a different class than DMT taken during the previous year (n = 55).

**Main Outcomes and Measures:** The primary end point was disease progression, defined as an EDSS score increase after at least 1 year of 1.0 point or more (minimal clinically important difference, 0.5) on 2 evaluations 6 months apart, with differences in time to progression estimated as hazard ratios.

**Results:** Among 110 randomized patients (73 [66%] women; mean age, 36 [SD, 8.6] years), 103 remained in the trial, with 98 evaluated at 1 year and 23 evaluated yearly for 5 years (median follow-up, 2 years; mean, 2.8 years). Disease progression occurred in 3 patients in the HSCT group and 34 patients in the DMT group. Median time to progression could not be calculated in the HSCT group because of too few events; it was 24 months (interquartile range, 18-48 months) in the DMT group (hazard ratio, 0.07; 95% CI, 0.02-0.24; P < .001). During the first year, mean EDSS scores decreased (improved) from 3.38 to 2.36 in the HSCT group and increased (worsened) from 3.31 to 3.98 in the DMT group (between-group mean difference, -1.7; 95% CI, -2.03 to -1.29; P < .001). There were no deaths and no patients who received HSCT developed nonhematopoietic grade 4 toxicities (such as myocardial infarction, sepsis, or other disabling or potential life-threatening events).

**Conclusions and Relevance:** In this preliminary study of patients with relapsing-remitting MS, nonmyeloablative HSCT, compared with DMT, resulted in prolonged time to disease progression. Further research is needed to replicate these findings and to assess long-term outcomes and safety.

**Association of occupational exposures with cardiovascular disease among US Hispanics/Latinos.**

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**OBJECTIVE:** Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in the USA. The role of occupational exposures to chemicals in the development of CVD has rarely been studied even though many agents possess cardiotoxic properties. We therefore evaluated associations of self-reported exposures to organic solvents, metals and pesticides in relation to CVD prevalence among diverse Hispanic/Latino workers.

**METHODS:** Cross-sectional data from 7404 employed individuals, aged 18-74 years, enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) were analysed. Participants from four US cities provided questionnaire data and underwent clinical examinations, including ECGs. CVD was defined as the presence of at least one of the following: coronary heart disease, atrial fibrillation, heart failure or cerebrovascular disease. Prevalence ratios reflecting the relationship between each occupational exposure and CVD as well as CVD subtypes were calculated using Poisson regression models.

**RESULTS:** Hispanic/Latino workers reported exposures to organic solvents (6.5%), metals (8.5%) and pesticides (4.7%) at their current jobs. Overall, 6.1% of participants had some form of CVD, with coronary heart disease as the most common (4.3%) followed by cerebrovascular disease (1.0%), heart failure (0.8%) and atrial fibrillation (0.7%). For individuals who reported working with pesticides, the prevalence ratios for any CVD were 2.18 (95% CI 1.34 to 3.55), coronary heart disease 2.20 (95% CI 1.31 to 3.71), cerebrovascular disease 1.38 (95% CI 0.62 to 3.03), heart failure 0.91 (95% CI 0.23 to 3.54) and atrial fibrillation 5.92 (95% CI 1.89 to 18.61) after adjustment for sociodemographic, acculturation, lifestyle and occupational characteristics. Metal exposures were associated with an almost fourfold (3.78, 95% CI 1.24 to 11.46) greater prevalence of atrial fibrillation. Null associations were observed for organic solvent exposures.

**CONCLUSIONS:** Our results suggest that working with metals and pesticides could be risk factors for CVD among Hispanic/Latino workers. Further work is needed to evaluate these relationships prospectively.