

## **IACFS/ME Newsletter January 2017 Abstracts Roundup - Compiled by Dr. Ros Vallings**

### **Gastrointestinal disease and microbial translocation in patients with systemic sclerosis: An observational study on the effect of nutritional intervention and implications for the role of the microbioma in the pathogenesis of the disease**

Authors: Luchetti MM et al.

Summary: This study had the broad and ambitious aims of evaluating serum biomarkers for monitoring gastrointestinal (GI) disease in scleroderma with and without dietary intervention to determine whether altering the gut microbiome influenced autoimmune disease. Various biomarkers were measured in 25 healthy controls and in 38 scleroderma patients with GI involvement at baseline and after 6 months of changing to a diet low in meat and dairy products. At baseline, levels of soluble CD14 (sCD14, a marker of immune system activation), lipopolysaccharide (LPS, a marker of microbial translocation) and intestinal-type fatty acid-binding protein (I-FABP, a marker of enterocyte damage) were significantly higher in scleroderma patients than in healthy controls. There was a strong correlation between sCD14/ I-FABP and LPS/I-FABP in the serum of scleroderma patients. After 6 months of dietary intervention there was a reduction in all three biomarkers in the scleroderma patients and a marked improvement in GI symptoms, wellbeing and quality of life.

Comment: This study demonstrates that markers of microbial translocation and immune activation are elevated in scleroderma patients with GI involvement, and that dietary intervention was associated with improvements in biomarker levels as well as symptoms. It provides support for dietary intervention in scleroderma patients with GI symptoms and hints at a possible role of the gut microbiome in the immunopathogenesis of scleroderma.

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# Computer-based-limited and personalised education management maximise appropriateness of vitamin D, vitamin B12 and folate retesting

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## Abstract

**Aim** To identify the best management strategy for improving the appropriateness of vitamin D, vitamin B12 and folate retesting.

**Methods** The study was conducted between 3 November 2012 and 8 June 2015, with inpatients and outpatients being considered separately. After an observational reference period (3 November 2012 to 14 September 2013), an information technology (IT)-based permissive strategy (16 September 2013 to 27 July 2014) followed by a limiting strategy was used to manage the demand for inpatient retesting. For outpatients, an educational strategy period (28 July 2014 to 16 December 2014) with direct contact between medical personnel and general practitioners (GPs) was followed by a post-educational period without any restriction. Data from a total of 66 496 patients for vitamin D, 14 618 for vitamin B12 and 14 445 for folate were retrieved from the laboratory IT system. The main outcomes measures were inappropriate vitamin D, vitamin B12 and folate retesting. The minimal retesting intervals were 90 (vitamin D) or 180 days (vitamin B12 and folate).

**Results** In the absence of a laboratory demand strategy, the frequency of inappropriate retesting for vitamin D, vitamin B12 and folate was 60%, 94% and 93%, respectively, for inpatients, and 27%, 87% and 87%, respectively, for outpatients. A limiting IT-based demand management strategy reduced inappropriate retesting for vitamin D (36%), but not for vitamin B12 and folate. The educational strategy was followed by a reduction in inappropriate retesting among outpatients (16% for vitamin D, 72% for vitamin B12 and folate).

**Conclusions** Laboratory demand management based on an IT-limiting management strategy or on education of the referring physicians appears helpful in maximising appropriate retesting.

## Immunologic Research pp 1-11

### Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature

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## Abstract

Human papilloma virus (HPV) is recognized as a major cause for cervical cancer among women worldwide. Two HPV vaccines are currently available: Gardasil<sup>®</sup> and Cervarix<sup>®</sup>. Both vaccines enclose viral antigenic proteins, but differ as to the biological systems of culture and the adjuvant components. Recently, a collection of symptoms, indicating nervous system dysfunction, has been described after HPV vaccination. We retrospectively described a case series including 18 girls (aged 12–24 years) referred to our “Second Opinion Medical Network” for the evaluation of “neuropathy with autonomic dysfunction” after HPV vaccination. All girls complained of long-lasting and invalidating somatoform symptoms (including asthenia, headache, cognitive dysfunctions, myalgia, sinus tachycardia and skin rashes) that have developed 1–5 days ( $n = 11$ ), 5–15 days ( $n = 5$ ) and 15–20 days ( $n = 2$ ) after the vaccination. These cases can be included in the recently described immune dysfunction named autoimmune/inflammatory syndrome induced by adjuvants (ASIA). HPV vaccine, through its adjuvant component, is speculated to induce an abnormal activation of the immune system, involving glia cells in the nervous system too. Further researches should aim at defining the pathological and clinical aspects of these post-vaccination diseases and identifying a genetic background predisposing to these adverse reactions.

# Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention

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## Abstract

**Introduction** Melatonin has been studied in headache disorders. Amitriptyline is efficacious for migraine prevention, but its unfavourable side effect profile limits its use.

**Methods** A randomised, double-blind, placebo-controlled study was carried out. Men and women, aged 18–65 years, with migraine with or without aura, experiencing 2–8 attacks per month, were enrolled. After a 4-week baseline phase, 196 participants were randomised to placebo, amitriptyline 25 mg or melatonin 3 mg, and 178 took a study medication and were followed for 3 months (12 weeks). The primary outcome was the number of migraine headache days per month at baseline versus last month. Secondary end points were responder rate, migraine intensity, duration and analgesic use. Tolerability was also compared between groups.

**Results** Mean headache frequency reduction was 2.7 migraine headache days in the melatonin group, 2.2 for amitriptyline and 1.1 for placebo. Melatonin significantly reduced headache frequency compared with placebo ( $p=0.009$ ), but not to amitriptyline ( $p=0.19$ ). Melatonin was superior to amitriptyline in the percentage of patients with a greater than 50% reduction in migraine frequency. Melatonin was better tolerated than amitriptyline. Weight loss was found in the melatonin group, a slight weight gain in placebo and significantly for amitriptyline users.

**Conclusions** Melatonin 3 mg is better than placebo for migraine prevention, more tolerable than amitriptyline and as effective as amitriptyline 25 mg.

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# Use of Plant-Based Therapies and Menopausal Symptoms - A Systematic Review and Meta-analysis

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## Abstract

**Importance** Between 40% and 50% of women in Western countries use complementary therapies to manage menopausal symptoms.

**Objective** To determine the association of plant-based therapies with menopausal symptoms, including hot flashes, night sweats, and vaginal dryness.

**Data Sources** The electronic databases Ovid MEDLINE, EMBASE, and Cochrane Central were systematically searched to identify eligible studies published before March 27, 2016. Reference lists of the included studies were searched for further identification of relevant studies.

**Study Selection** Randomized clinical trials that assessed plant-based therapies and the presence of hot flashes, night sweats, and vaginal dryness.

**Data Extraction** Data were extracted by 2 independent reviewers using a predesigned data collection form.

**Main Outcomes and Measures** Hot flashes, night sweats, and vaginal dryness.

**Results** In total, 62 studies were identified, including 6653 individual women. Use of phytoestrogens was associated with a decrease in the number of daily hot flashes (pooled mean difference of changes,  $-1.31$  [95% CI,  $-2.02$  to  $-0.61$ ]) and vaginal dryness score (pooled mean difference of changes,  $-0.31$  [95% CI,  $-0.52$  to  $-0.10$ ]) between the treatment groups but not in the number of night sweats (pooled mean difference of changes,  $-2.14$  [95% CI,  $-5.57$  to  $1.29$ ]). Individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes (pooled mean difference of changes,  $-0.79$  [ $-1.35$  to  $-0.23$ ]) and vaginal dryness score (pooled mean difference of changes,  $-0.26$  [ $-0.48$  to  $-0.04$ ]). Several herbal remedies, but not Chinese medicinal herbs, were associated with an overall decrease in the frequency of vasomotor symptoms. There was substantial heterogeneity in quality across the available studies, and 46 (74%) of the included randomized clinical trials demonstrated a high risk of bias within 3 or more areas of study quality.

**Conclusions and Relevance** This meta-analysis of clinical trials suggests that composite and specific phytoestrogen supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.

# Elevated basal serum tryptase identifies a multisystem disorder associated with increased *TPSAB1* copy number

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Elevated basal serum tryptase levels are present in 4–6% of the general population, but the cause and relevance of such increases are unknown<sup>1, 2</sup>. Previously, we described subjects with dominantly inherited elevated basal serum tryptase levels associated with multisystem complaints including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility. Here we report the identification of germline duplications and triplications in the *TPSAB1* gene encoding  $\alpha$ -tryptase that segregate with inherited increases in basal serum tryptase levels in 35 families presenting with associated multisystem complaints. Individuals harboring alleles encoding three copies of  $\alpha$ -tryptase had higher basal serum levels of tryptase and were more symptomatic than those with alleles encoding two copies, suggesting a gene-dose effect. Further, we found in two additional cohorts (172 individuals) that elevated basal serum tryptase levels were exclusively associated with duplication of  $\alpha$ -tryptase-encoding sequence in *TPSAB1*, and affected individuals reported symptom complexes seen in our initial familial cohort. Thus, our findings link duplications in *TPSAB1* with irritable bowel syndrome, cutaneous complaints, connective tissue abnormalities, and dysautonomia.

## **Mortality In Patients With Myalgic Encephalomyelitis And Chronic Fatigue Syndrome.**

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**Abstract Background:** There is a dearth of research examining mortality in individuals with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). Some studies suggest there is an elevated risk of suicide and earlier mortality compared to national norms. However, findings are inconsistent as other researchers have not found significant increases in all-cause mortality for patients.

**Objective:** This study sought to determine if patients with ME or CFS are reportedly dying earlier than the overall population from the same cause.

**Methods:** Family, friends, and caregivers of deceased individuals with ME or CFS were recruited through social media, patient newsletters, emails, and advocate websites. This study analyzed data including cause and age of death for 56 individuals that had ME or CFS.

**Results:** The findings suggest patients in this sample are at a significantly increased risk of earlier all-cause (M = 55.9 years) and cardiovascular-related (M = 58.8 years) mortality, and they had a directionally lower mean age of death for suicide (M = 41.3 years) and cancer (M = 66.3 years) compared to the overall U.S. population [M = 73.5 (all-cause), 77.7 (cardiovascular), 47.4 (suicide), and 71.1 (cancer) years of age].

**Conclusions:** The results suggest there is an increase in risk for earlier mortality in patients with ME and CFS. Due to the small sample size, the findings should be replicated to determine if the directional differences for suicide and cancer mortality are significantly different from the overall U.S. population.

Source: <http://bit.ly/2dYeqi1>



# Randomized, Double-blind, Placebo-controlled Phase III Trial of Duloxetine Monotherapy in Japanese Patients With Chronic Low Back Pain

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## [Disclosures](#)

Spine. 2016;41(22):1709-1717.

## Abstract

**Study Design.** A 14-week, randomized, double-blind, multicenter, placebo-controlled study of Japanese patients with chronic low back pain (CLBP) who were randomized to either duloxetine 60 mg once daily or placebo.

**Objective.** This study aimed to assess the efficacy and safety of duloxetine monotherapy in Japanese patients with CLBP.

**Summary of Background Data.** In Japan, duloxetine is approved for the treatment of depression, diabetic neuropathic pain, and pain associated with fibromyalgia; however, no clinical study of duloxetine has been conducted for CLBP.

**Methods.** The primary efficacy measure was the change in the Brief Pain Inventory (BPI) average pain score from baseline to Week 14. Secondary efficacy measures included BPI pain (worst pain, least pain, pain right now), Patient's Global Impression of Improvement, Clinical Global Impressions of Severity, and Roland-Morris Disability Questionnaire, among other measures, and safety and tolerability.

**Results.** In total, 458 patients were randomized to receive either duloxetine (n = 232) or placebo (n = 226). The BPI average pain score improved significantly in the duloxetine group compared with that in the placebo group at Week 14 [ $-2.43 \pm 0.11$  vs.  $-1.96 \pm 0.11$ , respectively; between-group difference (95% confidence interval),  $-0.46$  [ $-0.77$  to  $-0.16$ ];  $P = 0.0026$ ]. The duloxetine group showed significant improvement in many secondary measures compared with the placebo group, including BPI pain (least pain, pain right now) (between-group difference:  $-1.69 \pm 0.10$ ,  $P = 0.0009$ ;  $-2.42 \pm 0.12$ ,  $P = 0.0230$ , respectively), Patient's Global Impression of Improvement ( $2.46 \pm 0.07$ ,  $P = 0.0026$ ), Clinical Global Impressions of Severity ( $-1.46 \pm 0.06$ ,  $P = 0.0019$ ), and Roland-Morris Disability Questionnaire ( $-3.86 \pm 0.22$ ,  $P = 0.0439$ ). Adverse events occurring at a significantly higher incidence in the duloxetine group were somnolence, constipation, nausea, dizziness, and dry mouth, most of which were mild or moderate in severity and were resolved or improved.

**Conclusion.** Duloxetine 60 mg was effective and well tolerated in Japanese CLBP patients.

# Estimating the disease burden of ME/CFS in the United States and its relation to research funding

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## Abstract

At the National Institutes of Health (NIH), burden of disease is an important factor in funding decisions along with such factors as scientific opportunity, the quality of the science, and the interest of researchers. Recent studies have quantified the burden for a number of diseases in the United States and the NIH has used that information to analyze how its own funding patterns correspond to disease burden. However, the burden of disease has not been quantified for myalgic encephalomyelitis, also called chronic fatigue syndrome (ME/CFS) and is often underestimated due to a lack of research and the misperceptions about the nature of the disease.

Using the limited information in the literature, this paper develops a preliminary estimate of the disease burden of ME/CFS in the United States, using the World Health Organization's Disability Adjusted Life Years (DALY) measure. The ME/CFS DALY estimate is then compared to the NIH's 2013 analysis of research funding versus DALY across other funded diseases in order to estimate a level of funding for ME/CFS that would be commensurate with disease burden.

Even given the limitations arising from sparse data, this analysis demonstrates that federal research funding for this disease is far less than what would be expected by the burden of the disease. We conclude that the annual research funding for ME/CFS would need to increase twenty-five fold or more to be commensurate with disease burden. This level of funding would best leverage the growing interest of researchers and the significant scientific opportunities that exist to understand the pathology of this disease and to advance diagnostics and treatments.

## Key words

chronic fatigue syndrome, disability adjusted life years, disease burden, myalgic encephalomyelitis