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New concepts in the management of restless legs syndrome

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Abstract

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED) is a neurological condition with an overall prevalence in adults of 5-10% in Europe and North America. It is characterised by strong feelings of restlessness and distressing paraesthesia-like sensations in the lower legs, particularly when at rest. The symptoms vary considerably in severity and frequency. RLS/WED has a variable clinical expression influenced by genetic, environmental, and medical factors. Research into the pathophysiology of RLS/WED has found that various genetic markers and existing dysfunctions in dopaminergic mechanisms and iron mechanisms play a central role. Until recently, the first line treatment of RLS/WED was with low dose dopamine agonists, with three drugs having been approved by the US Food and Drug Administration and the European Medicines Agency. However, the occurrence of dopaminergic augmentation and an overall increase in severity of symptoms during long term treatment with dopamine agonists is leading to a shift towards non-dopaminergic alternatives as initial treatments, and particularly to $\alpha_2\delta$ ligands. Recent international guidelines recommend, whenever possible, to start treatment with these drugs ($\alpha_2\delta$ ligands) to avoid augmentation from the start. Other (eg, glutamatergic or adenosine) neurotransmitters might also play an important role in causing RLS/WED and might thus lead to new treatments.

From good health to illness with postinfectious fatigue syndrome: a qualitative study of adults' experiences of the illness trajectory

Eva Stormorken^{1*}, Leonard A. Jason² and Marit Kirkevold¹

Abstract

Background: Municipal drinking water contaminated with the parasite *Giardia lamblia* in Bergen, Norway, in 2004 caused an outbreak of gastrointestinal infection in 2500 people, according to the Norwegian Prescription Database. In the aftermath a minor group subsequently developed post-infectious fatigue syndrome (PIFS). Persons in this minor group had laboratory-confirmed parasites in their stool samples, and their enteritis had been cured by one or more courses of antibiotic treatment. The study's purpose was to explore how the affected persons experienced the illness trajectory and various PIFS disabilities.

Methods: A qualitative design with in-depth interviews was used to obtain first-hand experiences of PIFS. To get an overall understanding of their perceived illness trajectory, the participants were asked to retrospectively rate their functional level at different points in time. A maximum variation sample of adults diagnosed with PIFS according to the international 1994 criteria was recruited from a cohort of persons diagnosed with PIFS at a tertiary Neurology Outpatient Clinic in Western Norway. The sample comprised 19 women and seven men (mean age 41 years, range 26–59). The interviews were fully transcribed and subjected to a qualitative content analysis.

Results: All participants had been living healthy lives pre-illness. The time to develop PIFS varied. Multiple disabilities in the physical, cognitive, emotional, neurological, sleep and intolerance domains were described. Everyone more or less dropped out from studies or work, and few needed to be taken care of during the worst period. The severity of these disabilities varied among the participants and during the illness phases. Despite individual variations, an overall pattern of illness trajectory emerged. Five phases were identified: prodromal, downward, turning, upward and chronic phase. All reached a nadir followed by varying degrees of improvement in their functional ability. None regained pre-illness health or personal and professional abilities.

Conclusions: The needs of persons with this condition are not met. Early diagnosis and interdisciplinary rehabilitation could be beneficial in altering the downward trajectory at an earlier stage, avoiding the most severe disability and optimising improvement. Enhanced knowledge among health professionals, tailored treatment, rest as needed, financial support and practical help would likely improve prognosis.

Keywords: Disability, Chronic fatigue syndrome, In-depth interview, Myalgic encephalomyelitis, Natural course, Patient experiences, Primary healthcare, Qualitative research *

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EULAR Revised Recommendations for the Management of Fibromyalgia

G J Macfarlane; C Kronisch; L E Dean; F Atzeni; W Häuser; E Fluß; E Choy; E Kosek; K Amris; J Branco; F Dincer; P Leino-Arjas; K Longley; G M McCarthy; S Makri; S Perrot; P Sarzi-Puttini; A Taylor; G T Jones

Ann Rheum Dis. 2017;76(2):318-328.

Abstract

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were 'expert opinion'.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only 'strong for' therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as 'weak for' based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

<https://www.ncbi.nlm.nih.gov/pubmed/28386004>

Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease

1. **Romain Bouziat et al**

Science 07 Apr 2017:

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DOI: 10.1126/science.aah5298

Viruses compound dietary pathology

Reoviruses commonly infect humans and mice asymptotically. Bouziat *et al.* found that immune responses to two gut-infecting reoviruses take different paths in mice (see the Perspective by Verdu and Caminero). Both reoviruses invoked protective immune responses, but for one reovirus, when infection happened in the presence of a dietary antigen (such as gluten or ovalbumin), tolerance to the dietary antigen was lost. This was because this strain prevented the formation of tolerogenic T cells. Instead, it promoted T helper 1 immunity to the dietary antigen through interferon regulatory factor 1 signaling. Celiac disease patients also exhibited elevated levels of antibodies against reovirus.

Science, this issue p. [44](#); see also p. [29](#)

Abstract

Viral infections have been proposed to elicit pathological processes leading to the initiation of T helper 1 (T_H1) immunity against dietary gluten and celiac disease (CeD). To test this hypothesis and gain insights into mechanisms underlying virus-induced loss of tolerance to dietary antigens, we developed a viral infection model that makes use of two reovirus strains that infect the intestine but differ in their immunopathological outcomes. Reovirus is an avirulent pathogen that elicits protective immunity, but we discovered that it can nonetheless disrupt intestinal immune homeostasis at inductive and effector sites of oral tolerance by suppressing peripheral regulatory T cell (pT_{reg}) conversion and promoting T_H1 immunity to dietary antigen. Initiation of T_H1 immunity to dietary antigen was dependent on interferon regulatory factor 1 and dissociated from suppression of pT_{reg} conversion, which was mediated by type-1 interferon. Last, our study in humans supports a role for infection with reovirus, a seemingly innocuous virus, in triggering the development of CeD.

New Horizons in Orthostatic Hypotension James Frith; Steve W. Parry
Age Ageing. 2017;46(2):168-174.

Abstract

Background: orthostatic hypotension (OH) is a common disabling condition associated with increased morbidity and mortality. Much of the evidence available is derived from younger populations with chronic neurological disease leading to uncertainty for the diagnosis and management of older people.

Objective: to provide an overview of recent and emerging evidence for the diagnosis, management and prognosis of OH in older persons.

Methods: a narrative review of recent studies, emerging therapies and relevant regulatory updates.

Findings: revisions to the diagnostic criteria for OH include the duration of the blood pressure drop, specific criteria for initial and delayed OH and OH with hypertension. Non-drug therapies remain the first-line treatment option and Comprehensive Geriatric Assessment appears to result in lower rates of OH. Recent evidence concerning withdrawal of causative medication is inconsistent. Midodrine has recently become the only licenced medication for OH in the UK. Other emerging treatments include atomoxetine and droxidopa but these require further evaluation. Many other agents may be used but are not supported by high-quality evidence. The increase in mortality associated with OH is less apparent in older people.

Summary: OH remains common in older people, the new diagnostic criteria address some of the previous uncertainty but evidence concerning withdrawal of antihypertensives is conflicting. Midodrine is now the only licenced medication for OH in the UK, but non-drug therapies remain first line and fludrocortisone may be considered before midodrine. We may see other agents such as droxidopa becoming increasingly used over the coming years.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=The+Spectrum+and+Burden+of+Influenza-Associated+Neurological+Disease+in+Children%3A>

The Spectrum and Burden of Influenza-Associated Neurological Disease in Children: Combined Encephalitis and Influenza Sentinel Site Surveillance from Australia 2013–2015

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H. Marshall J. Clark E. Elliott R. Booy A. C. Cheng C. A. Jones
on behalf of the ACE study investigators, FluCAN investigators and PAEDS network.

Clin Infect Dis cix412.

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Abstract

There are few longitudinal studies of seasonal influenza associated neurological disease (IAND) and none from the Southern hemisphere.

Methods.

We extracted prospectively acquired Australian surveillance data from two studies nested within the Paediatric Active Enhanced Disease Surveillance (PAEDS) network: the Influenza Complications Alert Network (FluCAN) study and the Australian Childhood Encephalitis (ACE) study between 2013 and 2015. We described the clinical features and severity of IAND in children, including influenza associated encephalitis/encephalopathy (IAE). We calculated the proportion of hospitalised influenza that is associated with IAND and IAE, and incidence of IAE.

Results.

Over three influenza seasons, we identified 54 cases of IAND at two tertiary children's hospitals from Australia that accounted for 7.6% of hospitalised influenza. These included 10 cases of IAE (1.4% hospitalised influenza). The mean annual incidence of IAE amongst Australian children (aged ≤ 14 years) was 2.8 per 1 000 000. The spectrum of IAND was broad and included: IAE (10) including distinct acute encephalopathy syndromes, simple febrile seizures (14), other seizures (16), acute ataxia (4), and other sub-acute syndromes (transverse myelitis (1), opsoclonus myoclonus (1)). Two thirds of children with IAND were aged ≤ 4 years; less than half had pre-existing neurological disease or other risk factors for severe influenza. IAE caused death or neurological morbidity in half of cases.

Conclusions.

Seasonal influenza is an important cause of acute neurological disease in Australian children. The spectrum of seasonal IAND appears similar to that described during the 2009 H1N1 pandemic. IAE is associated with high morbidity and mortality.

[https://www.ncbi.nlm.nih.gov/pubmed/?term=Pregabalin+Is+Effective+in+Reducing+Fibromyalgia+Pain+Charles+Argoff+Evid+Based+Med.+2017%3B22\(2\)%3A70-71.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pregabalin+Is+Effective+in+Reducing+Fibromyalgia+Pain+Charles+Argoff+Evid+Based+Med.+2017%3B22(2)%3A70-71.)

Pregabalin Is Effective in Reducing Fibromyalgia Pain

Charles Argoff

Evid Based Med. 2017;22(2):70-71.

Context

Anticonvulsants have been widely used in pain management for more than 50 years. Published neuropathic pain treatment guidelines have suggested their use, especially for neuropathic pain.^[1] The review by Derry *et al* focuses on the use of one such agent, pregabalin, in the treatment of fibromyalgia, an accepted and validated but heterogeneous condition in which diagnosis is made through history, physical examination and the exclusion of other diseases explaining the key symptoms. Methods

This was a systematic review of randomised, double-blind trials lasting 8 weeks or longer comparing either pregabalin to placebo or an active treatment for the treatment of pain in fibromyalgia. The Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched for randomised controlled trials from inception to 16 March 2016 for this update. Reference lists of retrieved studies and reviews were also searched, and online clinical trial registries. Eight studies were included in this review and none of the included studies involved an active comparator. It is important to note that this systematic review and meta-analysis does not comment on how the diagnosis of fibromyalgia was made in the studies included.

Findings

More people using pregabalin 300–600 mg daily compared with placebo achieved either 30% or 50% pain intensity reduction on the Patient Global Impression of Change scale. Nine per cent more patients using pregabalin 300–600 mg/day compared with placebo achieved at least 50% pain reduction and 11% more patients using similar doses of pregabalin achieved at least 30% pain reduction. The majority of participants in each treatment group experienced adverse effects (70–90%), with dizziness (38%), somnolence (23%), weight gain (9%) and peripheral oedema (8%) occurring most frequently. The authors concluded that the magnitude of benefit of pregabalin is similar to minalcipran and duloxetine, two other medications used to treat fibromyalgia.

Comments

The authors note that fibromyalgia is a heterogeneous condition and that the use of pregabalin is associated with a major reduction in pain intensity for only a small proportion of people. There is no attempt in the review to identify subpopulations of patients with fibromyalgia that may be more or less responsive to treatment with pregabalin. While the authors noted that 'recent research points at small fibre pathology in a subgroup of fibromyalgia patients that may be of pathophysiological importance', the authors in the same sentence continue, 'though this is regarded as speculative'. The authors cite two references to support the presence of small fibre pathology in patients previously diagnosed with fibromyalgia according to the 2010 ACR criteria; however, quite shockingly, do not cite any references to support that these findings derived from formal analysis are speculative. In fact, in Oaklander *et al*'s^[2] study, 27 patients with fibromyalgia were compared with 30 controls, and 41% of patients with fibromyalgia compared with 3% of controls, demonstrated skin biopsy findings (intraepidermal skin fibre density reduction) consistent with the diagnosis of small fibre polyneuropathy (SFPN). In Üçeyler *et al*'s^[3] study, more patients with fibromyalgia compared with depressed or control patients had demonstrated SFPN changes based on a number of assessments, including skin biopsy. One should not describe these observations as speculative, and therefore, the authors of this Cochrane review demonstrate bias in using the term speculative when the data suggest otherwise. The authors would have been correct in stating that no reviewed study documented a subgroup analysis based on the presence or absence of skin biopsy findings consistent with SFPN. The published results from two studies that SFPN is prevalent in patients diagnosed with fibromyalgia is not speculative; instead, it should call into question just how appropriate the diagnosis of fibromyalgia is in such patients. That key point is missing from this review and significantly limits its clinical relevance and integrity.

Implications for Practice

Evidence-based medicine has been described as the 'conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research'.^[4] This review departs from these foundations of evidence-based medicine not only by relying on population-based studies only in arriving at their conclusions for clinicians, but also by the authors' dismissal of the results noted in studies that they referenced, of a significant prevalence of SFPN in patients previously diagnosed with fibromyalgia. This dismissal is at odds with how they define fibromyalgia in their 'description of the condition'. Such dismissal does not assist those in practice to best understand their patient's condition(s) and could impair their ability to make important treatment decisions about individual patients. Instead, practicing clinicians, academic clinicians and other academicians who conduct clinical trials only should all, in an unbiased manner, integrate the data regarding the prevalence of SFPN in patients who meet the 2010 American College of Rheumatology criteria for fibromyalgia into their assessment, treatment and investigational approaches to the patients who they are evaluating for fibromyalgia. While there is currently a dearth of published meaningful clinical trials regarding the treatment of SFPN, future efforts need to embrace, not hide, the need to precisely define patient populations so that the information gained from the results of future trials can truly be applied to the patients who we treat in our daily practice.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=BMJ+2017%3B357%3Aj1284>

Management of chronic pain using complementary and integrative medicine

BMJ 2017; 357 doi: <https://doi.org/10.1136/bmj.j1284> (Published 24 April 2017) Cite this as: *BMJ* 2017;357:j1284

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Abstract

Complementary and integrative medicine (CIM) encompasses both Western-style medicine and complementary health approaches as a new combined approach to treat a variety of clinical conditions. Chronic pain is the leading indication for use of CIM, and about 33% of adults and 12% of children in the US have used it in this context. Although advances have been made in treatments for chronic pain, it remains inadequately controlled for many people. Adverse effects and complications of analgesic drugs, such as addiction, kidney failure, and gastrointestinal bleeding, also limit their use. CIM offers a multimodality treatment approach that can tackle the multidimensional nature of pain with fewer or no serious adverse effects. This review focuses on the use of CIM in three conditions with a high incidence of chronic pain: back pain, neck pain, and rheumatoid arthritis. It summarizes research on the mechanisms of action and clinical studies on the efficacy of commonly used CIM modalities such as acupuncture, mind-body system, dietary interventions and fasting, and herbal medicine and nutrients.

<http://www.medscape.com/viewarticle/881527>

Bright-Light Treatment Shows Promise for Fibromyalgia

Megan Brooks Medscape Family Medicine

June 13, 2017

BOSTON — Morning bright-light treatment may be an effective adjunctive treatment for fibromyalgia, improving function and easing pain sensitivity, perhaps by shifting sleep patterns in a way that appears to help fibromyalgia, results of a pilot study suggest. Helen J. Burgess, PhD, director, Biological Rhythms Research Laboratory and professor, Department of Behavioral Sciences, Rush University Medical Center in Chicago, Illinois, presented the study here at SLEEP 2017: 31st Annual Meeting of the Associated Professional Sleep Societies.

Morning light treatment has been shown to reduce depression. Moreover, improved mood can lead to diminished pain and improvement in people's ability to cope and function with pain.

Dr Burgess and colleagues tested the effect of bright-light treatment on function and pain sensitivity in 10 women meeting American College of Rheumatology 2010 criteria for fibromyalgia.

The women slept at home, keeping their usual sleep schedule for 1 week, followed by an overnight session in the sleep lab. During the overnight session, the researchers assessed baseline function (Fibromyalgia Impact Questionnaire [FIQ]), pain sensitivity (heat threshold and tolerance), and circadian timing (dim-light melatonin onset).

The following morning, the women were randomly assigned to 6 days of a self-administered home morning (n = 6) or evening (n = 4) light treatment, using light boxes 1 hour per day. Afterward, function, pain sensitivity, and circadian timing were reassessed.

On average, the women completed 84% of the scheduled light treatments. No side effects were reported.

Both morning and evening light treatments led to improvements in function and pain sensitivity, but only morning light treatment led to a clinically meaningful improvement in function (>14% reduction in FIQ) and heat pain threshold ($P < .05$).

Examination of an internet-delivered cognitive behavioural pain management course for adults with fibromyalgia: a randomized controlled trial

Friesen, Lindsay N.; Hadjistavropoulos, Heather D.; Schneider, Luke H.; Alberts, Nicole M.; Titov, Nikolai; Dear, Blake F.

doi: 10.1097/j.pain.0000000000000802

Abstract: Fibromyalgia (FM) is a common and often debilitating chronic pain condition. Research shows that symptoms of depression and anxiety are present in up to 3 quarters of individuals with FM. Of concern, most adults with FM cannot access traditional face-to-face cognitive behavioural pain management programs, which are known to be beneficial. Given known difficulties with treatment access, the present study sought to explore the efficacy and acceptability of a previously developed Internet-delivered cognitive behavioural pain management course, the *Pain Course*, for adults with FM. The five-lesson course was delivered over 8 weeks and was provided with brief weekly contact, via telephone and secure email, with a guide throughout the course. Participants were randomized either to the *Pain Course* (n = 30) or to a waiting-list control group (n = 30). Symptoms were assessed at pre-treatment, post-treatment and 4-week follow-up. Completion rates (87%) and satisfaction ratings (86%) were high. Improvements were significantly greater in treatment group participants compared to waiting-list group participants on measures of FM (Cohen's $d = 0.70$; 18% reduction), depression (Cohen's $d = 0.63-0.72$; 20%-28% reduction), pain (Cohen's $d = 0.87$; 11% improvement) and fear of pain (Cohen's $d = 1.61$; 12% improvement). Smaller effects were also observed on measures of generalized anxiety and physical health. The changes were maintained at 4-week follow-up. The current findings add to existing literature and highlight the specific potential of Internet-delivered cognitive behavioural pain management programs for adults with FM, especially as a part of stepped-care models of care. Future research directions are described.

A guided Internet-delivered cognitive behavioural pain management course for fibromyalgia found improved fibromyalgia, depression, pain and fear of pain relative to waiting list control.

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<http://bit.ly/2rqF2RE>

Strenuous Exercise Can Cause Significant GI Symptoms

Aliment Pharmacol Ther 2017

By Will Boggs MD

June 26, 2017

NEW YORK (Reuters Health) - Strenuous exercise can result in gastrointestinal injury and symptoms, according to the authors of a systematic review.

"Moderate to vigorous exercise over two hours has consistently been shown to significantly damage the gut and is associated with increased incidence and severity of gastrointestinal symptoms," Dr. Ricardo J. S. Costa from Monash University, Notting Hill, Victoria, Australia told Reuters Health by email.

Exercise, while beneficial for prevention and management of various diseases, can be associated with exercise-induced gastrointestinal syndrome, which refers to disturbances of gastrointestinal integrity and function.

When Dr. Costa and colleagues analyzed data from healthy populations and patients with chronic gastrointestinal conditions, they found that increased exercise intensity and duration are associated with increases in measures of intestinal injury, permeability, and endotoxemia, as well as impairment of gastric emptying, slowing of small intestinal transit, and malabsorption.

All these markers of gastrointestinal disturbance can be exacerbated by the addition of heat stress and particularly during running, they noted online June 7th in *Alimentary Pharmacology and Therapeutics*.

It is unclear from the literature whether individuals with gastrointestinal conditions have a greater incidence or severity of exercise-induced gastrointestinal syndrome compared with healthy counterparts, they add. Furthermore, there has been no research on the prevention and management of exercise-induced gastrointestinal syndrome in patients with these conditions.

What is clear is that gastrointestinal symptoms developing during exercise invariably resolve, the authors emphasize.

For prevention, they recommend starting exercise hydrated and maintaining hydration throughout, optimizing carbohydrate consumption during exercise, and avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) before exercise.

A low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet might also be beneficial, but blinded studies have not found a gluten-free diet to be beneficial in non-celiac athletes.

"If athletes present with exercise-associated gastrointestinal symptoms, it is important to refer for a gut assessment during exercise to establish the individual causal mechanism of exercise-induced gastrointestinal syndrome," Dr. Costa said.

His advice: "Participate in exercise within individual comfort zone and allow sufficient recovery time between sessions."

Dr. Tanja Oosthuyse from University of Witwatersrand Medical School, Johannesburg, South Africa, who has published extensively on exercise and its effects, emailed to Reuters Health her advice for athletes who want to reduce the risk of GI symptoms.

-Ensure the last meal is ingested at least 2 h before exercise.

-Ensure carbohydrate supplement beverages are not too concentrated, i.e., not greater than 8% carbohydrate (CHO) solution.

-Maintain euhydration during exercise and include electrolytes to prevent hyponatremia.

-In hot conditions, when splanchnic blood flow may be restricted, reduce carbohydrate intake slightly.

-Use cooling strategies, such as ingesting sports drinks with crushed ice and frequently cooling the neck and head, to help reduce the central perception of thermal stress and possibly lessen the restriction on splanchnic blood flow.

-Avoid ingesting low glycemic index carbohydrates during exercise because they have increased intestinal retention time and cause increased intestinal fluid retention resulting in severe GI symptoms.

-Regular ingestion of CHO supplements during training will upregulate intestinal CHO transport and absorption pathways.

-Never ingest NSAIDS during prolonged exercise.

-Carefully regulate exercise intensity during prolonged exercise sessions to ensure that the proportion of time exercising at a high intensity above lactate threshold is controlled (less than 10% of exercise time in very long exercise bouts).

-Runners with frequent GI symptoms should consider cross training with cycling to reduce episodes of intestinal injury.

SOURCE: <http://bit.ly/2rqF2RE> Aliment Pharmacol Ther 2017.

[https://www.ncbi.nlm.nih.gov/pubmed/?term=Morbidity+and+Mortality+Weekly+Report.+2017%3B66\(23\)%3A607-609](https://www.ncbi.nlm.nih.gov/pubmed/?term=Morbidity+and+Mortality+Weekly+Report.+2017%3B66(23)%3A607-609)

Serious Bacterial Infections Acquired During Treatment of Patients Given a Diagnosis of Chronic Lyme Disease — United States

Natalie S. Marzec, MD; Christina Nelson, MD; Paul Ravi Waldron, MD; Brian G. Blackburn, MD; Syed Hosain, MD; Tara Greenhow, MD; Gary M. Green, MD; Catherine Lomen-Hoerth, MD, PhD; Marjorie Golden, MD; Paul S. Mead, MD

[DISCLOSURES](#)

Morbidity and Mortality Weekly Report. 2017;66(23):607-609.
Abstract and Introduction

Introduction

The term "chronic Lyme disease" is used by some health care providers as a diagnosis for various constitutional, musculoskeletal, and neuropsychiatric symptoms.^[1,2] Patients with a diagnosis of chronic Lyme disease have been provided a wide range of medications as treatment, including long courses of intravenous (IV) antibiotics.^[3,4] Studies have not shown that such treatments lead to substantial long-term improvement for patients, and they can be harmful.^[1,5] This report describes cases of septic shock, osteomyelitis, *Clostridium difficile* colitis, and paraspinal abscess resulting from treatments for chronic Lyme disease. Patients, clinicians, and public health practitioners should be aware that treatments for chronic Lyme disease can carry serious risks.

Lyme disease is a well-known condition caused by infection with the spirochete *Borrelia burgdorferi* sensu lato. Features of early infection include erythema migrans (an erythematous skin lesion with a bull's-eye or homogeneous appearance), fever, headache, and fatigue. If left untreated, the spirochete can disseminate throughout the body to cause meningitis, carditis, neuropathy, or arthritis.^[5,6] The recommended treatment for Lyme disease is generally a 2–4-week course of antibiotics.^[5]

Chronic Lyme disease, on the other hand, is a diagnosis that some health care providers use to describe patients with a variety of conditions such as fatigue, generalized pain, and neurologic disorders. Many of these patients have experienced significant debilitation from their symptoms and have not found relief after consultation with conventional medical practitioners. As a result, some seek treatment from practitioners who might identify themselves as Lyme disease specialists ("Lyme literate" doctors) or from complementary and alternative medicine clinics, where they receive a diagnosis of chronic Lyme disease.^[3,7]

A diagnosis of chronic Lyme disease might be based solely on clinical judgment and without laboratory evidence of *B. burgdorferi* infection, objective signs of infection, or a history of possible tick exposure in an area with endemic Lyme disease.^[1,7] There is a belief among persons who support the diagnosis and treatment of chronic Lyme disease that *B. burgdorferi* can cause disabling symptoms even when standard testing is negative, despite evidence that the recommended two-tiered serologic testing is actually more sensitive the longer *B. burgdorferi* infection has been present.^[6] Some practitioners use tests or testing criteria that have not been validated for the diagnosis of Lyme disease.^[1] A significant concern is that after the diagnosis of chronic Lyme disease is made, the actual cause of a patient's symptoms might remain undiagnosed and untreated.^[3,8]

Patients given a diagnosis of chronic Lyme disease have been prescribed various treatments for which there is often no evidence of effectiveness, including extended courses of antibiotics (lasting months to years), IV infusions of hydrogen peroxide, immunoglobulin therapy, hyperbaric oxygen therapy, electromagnetic frequency treatments, garlic supplements, colloidal silver, and stem cell transplants.^[1,3] At least five randomized, placebo-controlled studies have shown that prolonged courses of IV antibiotics in particular do not substantially improve long-term outcome for patients with a diagnosis of chronic Lyme disease and can result in serious harm, including death*.^[1,5,9]

Clinicians and state health departments periodically contact CDC concerning patients who have acquired serious bacterial infections during treatments for chronic Lyme disease. Five illustrative cases described to CDC over the past several years are presented.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Fecal+metagenomic+profiles+in+subgroups+of+patients+with+myalgic+encephalomyelitis%2Fchronic+fatigue+syndrome>

Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome

Dorottya Nagy-Szakal, Brent L. Williams, Nischay Mishra, Xiaoyu Che, Bohyun Lee, Lucinda Bateman, Nancy G. Klimas, Anthony L. Komaroff, Susan Levine, Jose G. Montoya, Daniel L. Peterson, Devi Ramanan, Komal Jain, Meredith L. Eddy, Mady Hornig and W. Ian Lipkin *Microbiome* 2017; 5:44

Background Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by unexplained persistent fatigue, commonly accompanied by cognitive dysfunction, sleeping disturbances, orthostatic intolerance, fever, lymphadenopathy, and irritable bowel syndrome (IBS). The extent to which the gastrointestinal microbiome and peripheral inflammation are associated with ME/CFS remains unclear. We pursued rigorous clinical characterization, fecal bacterial metagenomics, and plasma immune molecule analyses in 50 ME/CFS patients and 50 healthy controls frequency-matched for age, sex, race/ethnicity, geographic site, and season of sampling.

Results Topological analysis revealed associations between IBS co-morbidity, body mass index, fecal bacterial composition, and bacterial metabolic pathways but not plasma immune molecules. IBS co-morbidity was the strongest driving factor in the separation of topological networks based on bacterial profiles and metabolic pathways. Predictive selection models based on bacterial profiles supported findings from topological analyses indicating that ME/CFS subgroups, defined by IBS status, could be distinguished from control subjects with high predictive accuracy. Bacterial taxa predictive of ME/CFS patients with IBS were distinct from taxa associated with ME/CFS patients without IBS. Increased abundance of unclassified Alistipes and decreased Faecalibacterium emerged as the top biomarkers of ME/CFS with IBS; while increased unclassified Bacteroides abundance and decreased Bacteroides vulgatus were the top biomarkers of ME/CFS without IBS. Despite findings of differences in bacterial taxa and metabolic pathways defining ME/CFS subgroups, decreased metabolic pathways associated with unsaturated fatty acid biosynthesis and increased atrazine degradation pathways were independent of IBS co-morbidity. Increased vitamin B6 biosynthesis/salvage and pyrimidine ribonucleoside degradation were the top metabolic pathways in ME/CFS without IBS as well as in the total ME/CFS cohort. In ME/CFS subgroups, symptom severity measures including pain, fatigue, and reduced motivation were correlated with the abundance of distinct bacterial taxa and metabolic pathways.

Conclusions Independent of IBS, ME/CFS is associated with dysbiosis and distinct bacterial metabolic disturbances that may influence disease severity. However, our findings indicate that dysbiotic features that are uniquely ME/CFS-associated may be masked by disturbances arising from the high prevalence of IBS co-morbidity in ME/CFS. These insights may enable more accurate diagnosis and lead to insights that inform the development of specific therapeutic strategies in ME/CFS subgroups. **Keywords** Myalgic encephalomyelitis - Chronic fatigue syndrome - Microbiota-gut-brain axis - Metagenomic - Topological data analysis - Irritable bowel syndrome - Metabolic pathway

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Immune+network+analysis+of+cerebrospinal+fluid+in+myalgic+encephalomyelitis%2Fchronic+fatigue+syndrome+with+atypical+and+classical+presentations>

Immune network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome with atypical and classical presentations Hornig M, Gottschalk CG, Eddy ML, Che X, Ukaigwe JE, Peterson DL, Lipkin WI *Translational Psychiatry* 2017;7(4)

ABSTRACT Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a persistent and debilitating disorder marked by cognitive and sensory dysfunction and unexplained physical fatigue. Classically, cases present after a prodrome consistent with infection; however, some cases are atypical and have a different presentation and comorbidities that pose challenges for differential diagnosis. We analyzed cerebrospinal fluid (CSF) from 32 cases with classical ME/CFS and 27 cases with atypical ME/CFS using a 51-plex cytokine assay. Atypical subjects differed in cytokine profiles from classical subjects. In logistic regression models incorporating immune molecules that were identified as potential predictor variables through feature selection, we found strong associations between the atypical ME/CFS phenotype and lower CSF levels of the inflammatory mediators, interleukin 17A and CXCL9. Network analysis revealed an absence of inverse inter-cytokine relationships in CSF from atypical patients, and more sparse positive intercorrelations, than classical subjects. Interleukin 1 receptor antagonist appeared to be a negative regulator in classical ME/CFS, with patterns suggestive of disturbances in interleukin 1 signaling and autoimmunity-type patterns of immune activation. Immune signatures in the central nervous system of ME/CFS patients with atypical features may be distinct from those with more typical clinical presentations.

[https://www.ncbi.nlm.nih.gov/pubmed/?term=Activin+B+is+a+novel+biomarker+for+chronic+fatigue+syndrome%2Fmyalgic+encephalomyelitis+\(CFS%2FME\)+diagnosis%3A+a+cross+sectional+study](https://www.ncbi.nlm.nih.gov/pubmed/?term=Activin+B+is+a+novel+biomarker+for+chronic+fatigue+syndrome%2Fmyalgic+encephalomyelitis+(CFS%2FME)+diagnosis%3A+a+cross+sectional+study)

Activin B is a novel biomarker for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) diagnosis: a cross sectional study

Brett A. Lidbury, Badia Kita, Donald P. Lewis, Susan Hayward, Helen Ludlow, Mark P. Hedger and David M. de Kretser

Journal of Translational Medicine 2017; 15:60

Background Investigations of activin family proteins as serum biomarkers for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). CFS/ME is a disease with complex, wide-ranging symptoms, featuring persistent fatigue of 6 months or longer, particularly post exertion. No definitive biomarkers are available. Methods A cross-sectional, observational study of CFS/ME patients fulfilling the 2003 Canadian Consensus Criteria, in parallel with healthy non-fatigued controls, was conducted. Comparisons with a previously defined activin reference population were also performed. For the total study cohort the age range was 18–65 years with a female: male participant ratio of greater than 3:1. All participants were assessed via a primary care community clinic. Blood samples were collected for pathology testing after physical examination and orthostatic intolerance assessment. Cytokines, activin A, activin B and follistatin were also measured in sera from these samples. All data were compared between the CFS/ME and control cohorts, with the activins and follistatin also compared with previously defined reference intervals. Results Serum activin B levels for CFS/ME participants were significantly elevated when compared to the study controls, as well as the established reference interval. Serum activin A and follistatin were within their normal ranges. All routine and special pathology markers were within the normal laboratory reference intervals for the total study cohort, with no significant differences detected between CFS/ME and control groups. Also, no significant differences were detected for IL-2, IL-4, IL-6, IL-10, IL-17A, TNF or IFN-gamma.

Conclusion Elevated activin B levels together with normal activin A levels identified patients with the diagnostic symptoms of CFS/ME thus providing a novel serum based test. The activins have multiple physiological roles and capture the diverse array of symptoms experienced by CFS/ME patients. Keywords Myalgic encephalomyelitis (ME) - Chronic fatigue syndrome (CFS) – Biomarker - Activins - Diagnosis

<http://www.webmd.com/sleep-disorders/news/20170619/is-blue-light-bad-for-your-health>

Is Blue Light Bad for Your Health?

Lisa Marshall (Web Med)

July 05, 2017

Peek into the typical American household after dinner and you'll find the occupants bathed in a faint bluish glow. As parents fire off late emails on their laptops or lie in bed with eyes fixed on e-readers, kids update their Snapchat accounts or squeeze in one last game on their phones. Even if the gadgets are off, new eco-friendly street lamps, TVs, and household bulbs shine into the night, emitting a brighter, shorter-wavelength (more bluish), and more potent light than older incandescent bulbs did. All that concerns Charles Czeisler, PhD, MD, chief of the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital in Boston.

"The more research we do, the more evidence we have that excess artificial light at night can have a profound, deleterious effect on many aspects of human health," says Czeisler, who is also director of sleep medicine at Harvard Medical School. "It is a growing public health concern."

Czeisler is among a growing number of physicians, researchers, and health policy makers sounding the alarm that dark nights -- like a healthy diet, regular exercise, and good sleep habits -- are a key, endangered ingredient for long-term health.

Last year, the U.S. National Toxicology Program convened a 2-day workshop to explore mounting research linking exposure to artificial light at night not just to sleep problems, but also to weight gain, depression, cancer, and heart disease. In October, NASA went so far as to change all the lights on the International Space Station to ones that, as night falls, dim and change to longer-wavelength light, which has been shown to have less impact on human physiology than "blue light."

Last June, the American Medical Association chimed in. It issued a statement showing concerns that the new ultra-bright light-emitting diode (LED) lamps many cities are now using in their streetlights could "contribute to the risk of chronic disease."

Much of the research so far has been done on animals or comes from large population studies, which show patterns but don't confirm cause and effect. But many health experts say the results are troublesome enough to warrant action now.

"As opposed to the many other kinds of harmful environmental pollutants out there, we are rapidly figuring out exactly what to do about this one, and it is really not that hard," says Richard Stevens, PhD, a University of Connecticut cancer epidemiologist and light-at-night researcher. Just dim the lights at night and tone down that blue, he says.

The Power of Light

Light is by far the most important synchronizer of human circadian rhythms, or body clocks, Czeisler says. Specialized cells in the retina are finely tuned to respond to the short-wavelength light that comes from a cloudless blue sky. As light rays hit those cells, they tell the brain to stop pumping out drowsiness-inducing melatonin and start making hormones like cortisol and ghrelin that wake us up and make us hungry.

At dusk, in an electricity-free world, the opposite happens. As light fades, the body begins to transition to "nighttime physiology," in which melatonin levels rise, body temperature drops, sleepiness grows, and hunger goes away. The time spent in this restful state, even if we are not actually sleeping, is restorative, Stevens says. Trouble is, in the modern world, we are bathed by lights that have the same potent wavelength that wakes us up to, so our transition to nighttime physiology has been delayed by hours.

As Stevens puts it, we are "darkness deprived."

The best-documented consequence, by far, of excess evening light exposure is short-term sleep disruption. In one study, people in a sleep lab who read from an e-reader at night saw their nighttime melatonin levels drop by 55% after 5 days, took longer to fall asleep, had less restorative rapid eye movement (REM) sleep, and felt more groggy the next day than those reading a paper book.

Another study, looking at teenagers, suggests they may be even more sensitive to light at night. Just an hour of exposure from a glowing device, like a phone, suppressed melatonin by 23%; 2 hours decreased it by 38%.

Sleep issues aside, light at night is now being accused of helping fuel weight gain and metabolic diseases. Studies show that people exposed to more bright light at night are hungrier and produce

less insulin, making it harder for them to turn those late-night snacks into fuel. As a result, it rests in the blood, where it makes diabetes more likely, or it's stored as fat.

One March 2016 study by University of Haifa researchers compared World Health Organization obesity data with military satellite images of nighttime lighting and found that the men and women who lived in the places most illuminated at night were also the most likely to be obese.

Animal studies at Ohio State University show that even exposure to relatively dim light -- about the brightness of a child's nightlight 3 feet from the eyes -- over 8 weeks has a measurable impact on the brain. It raises inflammation and lowers levels of a hormone that's key for promoting new brain cell growth. It also causes transmitters between neurons to wither.

The animals also showed "depressive like symptoms" and had memory problems, says study author Randy Nelson, chairman of the department of neuroscience at Ohio State University. While studies looking at the way light at night affects the human brain are only in their infancy, population studies of emergency room workers and oilfield workers chronically exposed to bright light at night show similar thinking and mood impairments, even if those workers are getting enough sleep, Nelson says. "This is not just a sleep problem. This is a problem of disruption of the entire circadian clock, and sleep is just one hand of that clock."

Research is young, but some studies suggest that chronic exposure to excess light at night may also fuel cancer, in part by lowering the levels of melatonin -- a known anti-cancer agent -- circulating in the blood. Female night shift workers have a 50% to 70% greater chance of developing breast cancer during their lifetime, says David Blask, MD, associate director of the Tulane University Center for Circadian Biology.

One recent study of 75,000 nurses, published in the American Journal of Preventive Medicine, found that those who worked the night shift for more than 5 years were 11% more likely to die early. Some European governments, with health risks in mind, now pay women night shift workers hazard pay.

<http://www.medscape.com/viewarticle/882127>

Does Acupuncture Work? A Quick Review of the Latest Evidence

Hansa Bhargava, MD
July 05, 2017

I'm Dr Hansa Bhargava, a medical advisor for Medscape and a practicing physician. Let's talk about the benefits of acupuncture.

Acupuncture, a staple of traditional Chinese medicine, which is becoming more popular in the Western world, uses very fine needles to stimulate various pressure points around the body and re-shift the body's balance of energy. The practice is also thought to improve blood flow and increase levels of the body's natural pain-relieving chemicals.

But does acupuncture work? Well, according to the research, it's more effective for some conditions than for others. Take pain, for example. A 2012 meta-analysis in the *Archives of Internal Medicine* concluded that the practice was moderately effective for chronic neck, lower back, and arthritic knee pain.^[1] A Cochrane review found some evidence that acupuncture may relieve pain during an acute migraine episode and may modestly reduce frequency.^[2] Another Cochrane report concluded that the practice is effective for treating chronic tension-type headaches.^[3]

For other conditions, the benefits of acupuncture may be more limited. Though some studies find that it modestly improves quality of life in people with allergies, it may not be the most cost-effective solution for allergic rhinitis.^[4] Acupuncture may help with cancer, especially cancer-induced nausea and vomiting.^[5] And if used in conjunction with opioids for cancer pain, it can reduce the opioid dose needed.^[6]

Other potential applications are still being investigated. Newly emerging evidence suggests that the practice might be useful for some people with [amnesic mild cognitive impairment](#), a condition that can precede dementia. A meta-analysis found that people who got this treatment scored better on cognitive tests than those who didn't receive it,^[7] but further study is needed to confirm a benefit.

Acupuncture is generally safe for your patients to try, provided that they see a licensed and trained practitioner.

The 2017 hormone therapy position statement of The North American Menopause Society

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Position Statement

Abstract: The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of HT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture. For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic reevaluation. For bothersome GSM symptoms not relieved with over-the-counter therapies and without indications for use of systemic HT, low-dose vaginal estrogen therapy or other therapies are recommended.

This NAMS position statement has been endorsed by Academy of Women's Health, American Association of Clinical Endocrinologists, American Association of Nurse Practitioners, American Medical Women's Association, American Society for Reproductive Medicine, Asociación Mexicana para el Estudio del Climaterio, Association of Reproductive Health Professionals, Australasian Menopause Society, Chinese Menopause Society, Colegio Mexicano de Especialistas en Ginecología y Obstetricia, Czech Menopause and Andropause Society, Dominican Menopause Society, European Menopause and Andropause Society, German Menopause Society, Groupe d'études de la ménopause et du vieillissement Hormonal, HealthyWomen, Indian Menopause Society, International Menopause Society, International Osteoporosis Foundation, International Society for the Study of Women's Sexual Health, Israeli Menopause Society, Japan Society of Menopause and Women's Health, Korean Society of Menopause, Menopause Research Society of Singapore, National Association of Nurse Practitioners in Women's Health, SOBRAC and FEBRASGO, SIGMA Canadian Menopause Society, Società Italiana della Menopausa, Society of Obstetricians and Gynaecologists of Canada, South African Menopause Society, Taiwanese Menopause Society, and the Thai Menopause Society. The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017. The British Menopause Society supports this Position Statement.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1001%2Fjamainternmed.2016.9261>

Effect of Magnesium Oxide Supplementation on Nocturnal Leg Cramps- A Randomized Clinical Trial

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- JAMA Intern Med.* 2017;177(5):617-623. doi:10.1001/jamainternmed.2016.9261

Key Points

Question Is magnesium oxide significantly more effective than placebo in reducing the frequency of nocturnal leg cramps?

Findings In this randomized clinical trial that included 94 adults, the mean number of nocturnal leg cramps per week decreased significantly in both the magnesium oxide and placebo groups, with no significant difference between the groups.

Meaning This trial suggests that magnesium oxide is not significantly better than placebo for alleviating nocturnal leg cramps.

Abstract

Importance Magnesium supplements are widely marketed for prophylaxis of nocturnal leg cramps (NLC) despite no evidence of significant benefit.

Objective To determine whether magnesium oxide is better than placebo for NLC prophylaxis.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled clinical trial of 2 weeks eligibility screening followed by 4 weeks of treatment was conducted in northern Israel, from February to October 2013. An intention-to-treat data analysis was performed from March 22, 2014, to April 17, 2016. We used a volunteer sample of community-dwelling individuals experiencing NLC, 21 years or older, with 4 or more documented episodes of NLC during 2 weeks of screening.

Interventions Capsules containing either magnesium oxide or a similar-looking placebo to be taken orally, once daily at bedtime for a period of 4 weeks.

Main Outcomes and Measures The primary outcome was the difference in the mean number of NLC per week between the screening and treatment phases. Secondary outcomes included severity and duration of NLC, quality of life, and quality of sleep.

Results Of the 166 volunteers, 72 (43%) were excluded, of whom 15 declined to participate and 57 did not meet the inclusion criteria. Of the 94 individuals (39% male; mean [SD] age, 64.9 [11.1] years) randomly assigned to magnesium oxide (48) or placebo (46), 6 did not complete the study protocol (3 in each group). Mean (SD) change of NLC was -3.41 (4.05) (from 7.84 [5.68] to 4.44 [5.66]) and -3.03 (4.53) (from 8.51 [5.20] to 5.48 [4.93]) per week in the magnesium oxide and placebo groups, respectively, a difference between groups of 0.38 (0.48) NLC per week ($P = .67$ in an intention-to-treat analysis). There were no between-group differences in the severity and duration of NLC, quality of life, or quality of sleep.

Conclusions and Relevance Oral magnesium oxide was not superior to placebo for older adults experiencing NLC. The decrease in the mean number of NLC per week, from the screening to the

treatment phase in both groups, is probably a placebo effect that may explain the wide use of magnesium for NLC.

Trial Registration [clinicaltrials.gov Identifier: NCT01709968](https://clinicaltrials.gov/ct2/show/study/NCT01709968)

<http://bit.ly/2tMbazm>

Treatable Menopause Symptoms Linked to Depression in Older Women

By Shereen Lehman

July 10, 2017

(Reuters Health) - Women over age 65 dealing with hot flashes and other treatable symptoms of low estrogen are more likely to also have moderate or severe depression, according to a large study in Australia.

Researchers found that women with depressive symptoms were also more likely to have money worries, caregiving responsibilities or chronic health conditions, suggesting there are many issues that could contribute to depression in this age group. Treatment for depression should therefore address the hormonal problems in this mix that are modifiable, the study team advised online June 19 in the journal *Menopause*.

"Other studies had already shown that when women were perimenopausal or early postmenopausal that there is an increased vulnerability to depressive symptoms," senior study author Susan Davis told Reuters Health by email.

"We were interested in whether hot flushes were indicative of heightened vulnerability - and we found this to be the case," said Davis, a researcher with the School of Public Health and Preventive Medicine at Monash University in Melbourne.

Davis and colleagues enrolled more than 1,500 mostly white women between the ages of 65 and 79 who were randomly selected from Australian voter rolls.

The women answered questionnaires that asked about life and financial circumstances, relationships, health problems and medication use. They also asked about post-menopausal symptoms including hot flashes, night sweats and pain during intercourse, as well as about depressive symptoms and recent use of anti-depressant medications.

One of every three women reported having hot flashes, which also increased their risk of depressive symptoms by 67 percent compared to women without hot flashes.

One in four women had used a psychotropic medication such as an antidepressant in the previous month.

Women with partners were about 40 percent less likely to have depression symptoms compared to women who were alone. Women who were employed had less than half the risk of depressive symptoms compared to women who were unemployed.

While hot flashes, vaginal dryness and pelvic floor dysfunction were each independently associated with depression risk, the study cannot prove that these or any other factors examined in the analysis cause depression.

Davis, however, said loss of estrogen could be a contributor. "Estrogen has major central effects in the brain and the sudden fall in estrogen at menopause can cause some women to become profoundly anxious (or depressed)," she said. "After childbirth the sudden drop in hormones can have the same effect."

Older women with hot flashes, vaginal dryness or pelvic floor concerns should be evaluated for depression, "particularly if they have financial housing issues or significant caregiving responsibilities," Dr. JoAnn Pinkerton, who wasn't involved in the study, told Reuters Health by email.

"Women going through the menopause are four times more likely to suffer from depression than women who are younger than 45," said Pinkerton, an obstetrician-gynecologist in Charlottesville, Virginia, and executive director of the North American Menopause Society

Depression is not anxiety, bouts of sadness, low mood or mood swings but a mental disorder defined by the feeling of extreme sadness lasting for more than two weeks, often with no specific cause, and which interferes with everyday life, Pinkerton said.

As far as treatment, evidence doesn't support hormone therapy as a first treatment of depression, although it is often used along with counseling or antidepressants, she noted.

"For more severe depression, antidepressant medications can be used to correct the chemical imbalance and some have been found to relieve hot flashes. If depression is severe, antidepressant medication is most effective when used in combination with counseling or psychotherapy," she said. For mild to moderate depression, herbal remedies such as St. John's wort, cognitive behavioral therapy and lifestyle changes may be helpful, such as prioritizing tasks, exercising, engaging in activities, recognizing the effect of stress on your mood, she said.

Women with a history of perimenopause-related depression that improves on hormone therapy need to be monitored after hormone therapy is stopped, as their depressive symptoms may recur, Pinkerton added.

<http://www.medscape.com/viewarticle/883038>

Menopause 2017.

Inflammatory Dietary Pattern Linked to Brain Aging

Pauline Anderson
July 17, 2017

From the Alzheimers Disease Conference.

LONDON – Researchers believe they have uncovered a key piece of the puzzle in the connection between diet and dementia.

They linked a specific dietary pattern to blood markers of inflammation. In addition, they showed that in elderly adults who followed such a dietary pattern, brain gray matter volume was less, and they had worse visuospatial cognitive function.

"We found that people who consume less omega 3, less calcium, vitamin E, vitamin D, and vitamin B5 and B2 have more inflammatory biomarkers," study investigator Yian Gu, PhD, Columbia University and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, New York City, told *Medscape Medical News*.

An inflammatory dietary pattern, said Dr Gu, "is bad for both the brain and cognition."

The study was presented here at the Alzheimer's Association International Conference (AAIC) 2017. Potential Target

Evidence cited by Dr Gu suggests that dietary factors such as fish, nuts, omega-3 polyunsaturated fatty acids, and folate, as well Mediterranean-type diets, are associated with lower risk for Alzheimer's disease (AD) and better brain health in the elderly. Other evidence, she said, shows that many foods and nutrients modulate inflammatory processes.

Other studies have linked chronic inflammation to an increased risk for AD. Dr Gu's group previously showed an association between increased C-reactive protein (CRP) and interleukin-6 (IL6) levels and worse cognition and smaller brain volumes.

But none of this research addressed whether diet affects brain and cognitive health by modulating inflammation.

"No study has formally tested whether the relationship of diet with cognition, or with the brain, is actually because of inflammation," said Dr Gu.

The new cross-sectional study included 330 elderly adults from the Washington Heights–Inwood Community Aging Project imaging study. In these participants, researchers carried out structural MRI scans and measured levels of the inflammatory biomarkers CRP and IL6.

Study participants completed a 61-item food frequency questionnaire that asked about nutrient intake during the past year.

From this information, the researchers used a statistical model to create the inflammation-related nutrient pattern (INP).

"The INP is basically a linear combination of 24 nutrients, each with a different weight on the INP," said Dr Gu. "For example, omega-3 is negatively 'loaded' – which is similar to 'correlated' – on this pattern. Lower consumption of omega-3 will contribute to a higher INP score."

Study participants also underwent neuropsychological testing that assessed memory, language, executive speed, and visuospatial function. From these test scores, the researchers calculated a composite mean cognition score for each participant.

The study showed that the INP was positively correlated with CRP level ($P = .009$) and IL6 level ($P < .0001$).

Those with fewer years of education had a relatively high INP. The INP was higher for African Americans ($P < .0001$) and Hispanics ($P = .003$) compared to whites.

The analysis uncovered a significant association between INP and visuospatial function ($P = .015$) and total gray matter volume ($P = .002$) after adjusting for age, sex, race/ethnicity, APOE4 status, calorie intake, body mass index, and vascular comorbidity.

The researchers determined that having a smaller brain gray matter volume might help explain why those who consume more inflammatory nutrients have worse visuospatial cognition.

This study is important because "now you have a linkage to measurable biological differences," said Keith Fargo, PhD, director of scientific programs at the Alzheimer's Association

AACE/ACE Now Update Guidelines for Menopause Treatment

Pam Harrison

July 19, 2017

Yet another position statement on the treatment of menopausal symptoms is urging physicians to individualize their approach to women seeking relief from the consequences of low estrogen levels, including hot flashes and genitourinary problems.

The latest American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) position statement [was published](#) in the July 2017 issue of *Endocrine Practice*. "AACE feels it is important to emphasize that one size doesn't fit all when it comes to treating women with menopause," Rhonda Cobin, MD, past president of AACE and a member of its reproductive endocrinology scientific committee, said in a statement. "Hormone replacement therapy (HRT) must be individualized based on a woman's age, time of onset of menopause, and other cardiovascular, metabolic, and genetic factors," she added.

The AACE committee notes that no recommendations from its previous guidelines in 2011 have been reversed or changed. However, "new information available from randomized clinical trials and epidemiologic studies reported after 2011 was critically reviewed," committee members state.

Among the new recommendations is a suggestion that transdermal rather than oral estrogen might be considered if physicians are concerned about a patient's thrombotic risk. Transdermal HRT might also reduce the risk of stroke and coronary artery disease, they indicate.

And "when the use of progesterone is necessary, micronized progesterone is considered the safer alternative," committee members note.

Similarly, women seeking relief from menopausal symptoms may benefit from the use of selective serotonin re-uptake inhibitors (SSRIs) and possibly other nonhormonal agents if HRT is judged to be too great a risk for an individual woman.

Specific Recommendations for Women With Breast Cancer

Of note, however, the committee cautions that certain SSRIs are contraindicated in patients taking tamoxifen for the prevention of breast cancer recurrence, a recommendation that supports management practices endorsed by the Comité de l'Évolution des Pratiques Oncologiques (CEPO) in Quebec. Physicians should avoid the use of paroxetine and fluoxetine in women on tamoxifen because these SSRIs may reduce the efficacy of the anticancer treatment, as CEPO observes. Rather, CEPO suggests that venlafaxine, citalopram, clonidine, gabapentin, and pregabalin may be used for the treatment of hot flashes in breast cancer patients taking tamoxifen.

Venlafaxine, paroxetine, citalopram, clonidine, gabapentin, and pregabalin may also be considered for the treatment of hot flashes in breast cancer patients not taking tamoxifen.

The AACE committee also notes that women who are at high risk of or have had breast cancer should not use black cohosh for the treatment of menopausal symptoms, a recommendation again supported by CEPO.

No Evidence to Support Bioidentical Compounded HRT

The AACE/ACE committee does not endorse the use of bioidentical hormones, the same recommendation they made in their 2011 position statement.

As the statement authors note, there is no evidence supporting manufacturers' claims that bioidentical products are any safer than their approved HRT counterparts, and there is a risk that patients will get either greater or lesser amounts of the biologically active hormone as there is often a lack of consistency in the content of compounded products.

Common compounded bioidentical hormones include tri-estrogens (estriol, estrone, estradiol in an 8:1:1 ratio), bi-estrogen (estriol, estradiol in a 4:1 or 9:1 ratio), estriol/progesterone (2–8 mg/day plus 100–200 mg/day), testosterone, and dehydroepiandrosterone.

Individualize HRT Therapy

Unlike the [recently published](#) position paper on HRT by the North American Menopause Society (NAMS), however, the AACE/ACE position paper does not specifically caution against introducing HRT in women who are 10 or more years out from the menopause, or those 60 years of age or older, for whom the risk of treatment may outweigh the benefits.

However, the committee did indicate that HRT is less likely to be harmful if introduced early on in the menopause rather than if used later on.

Nor does the AACE committee recommend physicians use HRT to prevent diabetes; in women with diabetes, the committee cautions that HRT be prescribed only after carefully considering its risk given the patient's age, as well as the presence of metabolic and cardiovascular risk factors.

"The updated position statement on menopause demonstrates AACE's commitment to individualizing our guidelines as much as current science permits for the betterment of patient care," Mack Harrell, MD, president of ACE said in a statement.

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Association of Antidepressant Medication Use During Pregnancy With Intellectual Disability in Offspring

Alexander Viktorin, PhD^{1,2,3}; Rudolf Uher, MD, PhD⁴; Alexander Kolevzon, MD^{1,2}; et al/Abraham Reichenberg, PhD^{1,2}; Stephen Z. Levine, PhD⁵; Sven Sandin, PhD^{1,2,3}

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Question Does maternal antidepressant medication use during pregnancy increase the risk of intellectual disability in offspring?

Findings In this population-based cohort study of 179 007 pregnancies, an association of maternal antidepressant medication use during pregnancy with intellectual disability in offspring was attenuated when parental factors other than medication use were taken into account.

Meaning An elevated risk of intellectual disability in children born to women who used antidepressant medication during pregnancy is likely attributable to factors underlying the treatment and not to the antidepressant medication itself.

Abstract

Importance Maternal antidepressant medication use during pregnancy has previously been associated with adverse outcomes in offspring, but to our knowledge, the association with intellectual disability (ID) has not been investigated.

Objectives To examine the association of maternal antidepressant medication use during pregnancy with ID in offspring and investigate the importance of parental mental illness for such an association.

Design, Setting, and Participants A population-based cohort study of 179 007 children born from January 1, 2006, through December 31, 2007, with complete parental information from national registers who were followed up from birth throughout 2014.

Main Outcomes and Measures We estimated relative risks (RRs) and 95% CIs of ID in children exposed during pregnancy to any antidepressant medication or specifically to selective serotonin reuptake inhibitor (SSRI) antidepressants, all other non-SSRI antidepressants, or other nonantidepressant psychotropic medications. Analyses were adjusted for potential confounders. In addition to full population analyses, we used a subsample to compare mothers who used antidepressants during pregnancy with mothers who had at least one diagnosis of depression or anxiety before childbirth but did not use antidepressants during pregnancy.

Results Of the 179 007 children included in the study (mean [SD] age at end of follow-up, 7.9 [0.6] years; 92 133 [51.5%] male and 86 874 [48.5%] female), ID was diagnosed in 37 children (0.9%) exposed to antidepressants and in 819 children (0.5%) unexposed to antidepressants. With adjustment for potential confounders, the RR of ID after antidepressant exposure was estimated at 1.33 (95% CI, 0.90-1.98) in the full population sample and 1.64 (95% CI, 0.95-2.83) in the subsample of women with depression. Results from analyses of SSRI antidepressants, non-SSRI antidepressants, and nonantidepressant psychotropic medications and analyses in the clinically relevant subsample did not deviate from the full-sample results.

Conclusions and Relevance The unadjusted RR of ID was increased in offspring born to mothers treated with antidepressants during pregnancy. After adjustment for confounding factors, however, the current study did not find evidence of an association between ID and maternal antidepressant medication use during pregnancy. Instead, the association may be attributable to a mechanism integral to other factors, such as parental age and mother's psychiatric disorder.

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Cytokine+signature+associated+with+disease+severity+in+chronic+fatigue+syndrome+patients>

Cytokine signature associated with disease severity in chronic fatigue syndrome patients

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Significance

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) devastates the lives of millions of people and has remained a mystery illness despite decades of research. It has long been suspected that inflammation is central to its pathogenesis. Although only two cytokines were found to be different (TGF- β higher and resistin lower) in ME/CFS patients compared with controls, 17 cytokines correlated with ME/CFS severity. Thirteen of these cytokines are proinflammatory and may contribute to many of the symptoms these patients experience for several years. Only CXCL9 (MIG) inversely correlated with fatigue duration.

Abstract

Although some signs of inflammation have been reported previously in patients with myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), the data are limited and contradictory. High-throughput methods now allow us to interrogate the human immune system for multiple markers of inflammation at a scale that was not previously possible. To determine whether a signature of serum cytokines could be associated with ME/CFS and correlated with disease severity and fatigue duration, cytokines of 192 ME/CFS patients and 392 healthy controls were measured using a 51-multiplex array on a Luminex system. Each cytokine's preprocessed data were regressed on ME/CFS severity plus covariates for age, sex, race, and an assay property of newly discovered importance: nonspecific binding. On average, TGF- β was elevated ($P = 0.0052$) and resistin was lower ($P = 0.0052$) in patients compared with controls. Seventeen cytokines had a statistically significant upward linear trend that correlated with ME/CFS severity: CCL11 (Eotaxin-1), CXCL1 (GRO α), CXCL10 (IP-10), IFN- γ , IL-4, IL-5, IL-7, IL-12p70, IL-13, IL-17F, leptin, G-CSF, GM-CSF, LIF, NGF, SCF, and TGF- α . Of the 17 cytokines that correlated with severity, 13 are proinflammatory, likely contributing to many of the symptoms experienced by patients and establishing a strong immune system component of the disease. Only CXCL9 (MIG) inversely correlated with fatigue duration.

Footnotes

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<https://www.ncbi.nlm.nih.gov/pubmed/?term=Fibromyalgia%2C+a+Missed+Comorbidity+in+Spondyloarthritis>

Fibromyalgia, a Missed Comorbidity in Spondyloarthritis

Prevalence and Impact on Assessment and Treatment

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Abstract

Purpose of review Fibromyalgia is a clinical representation of the neurobiological phenomenon of central sensitization, characterized by chronic widespread pain, fatigue, sleep disturbance, and other symptoms. Fibromyalgia may occur in conjunction with chronic rheumatic diseases, driven by the effects of chronic pain and inflammation and likely influenced by the patient's genetic and psychoemotional background. This article reviews the data on prevalence of concomitant fibromyalgia and its impact on disease assessment in patients with spondyloarthritis (SpA) and psoriatic arthritis (PsA).

Recent findings Fibromyalgia occurs in 2–8% of the general population. In AxSpA cohorts the prevalence has been reported in 4–25%, and in PsA, 16–22%, the majority being female. Measures of disease activity which are comprised partly or wholly of patient-reported outcomes such as pain and patient global are significantly higher in patients with concomitant fibromyalgia and do not improve as much with treatment as more objective measures, a finding which has been observed in other diseases such as rheumatoid arthritis and lupus.

Summary Fibromyalgia occurs in a significant proportion of patients with SpA and PsA. Disease activity measures with subjective elements are conflated in patients with fibromyalgia and do not reliably assess true inflammatory disease. This needs to be taken into account when evaluating the impact of immunomodulatory therapy.