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Internal Medicine

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ABSTRACT & COMMENTARY

No Single Solution to Prevent Medication Nonadherence

By David Fiore, MD

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Dr. Fiore reports no financial relationships relevant to this field of study.

SYNOPSIS: Simple, low-cost reminder pill bottles did not lead to more improvement in medication adherence in patients with documented poor adherence.

SOURCE: Choudhry NK, Krumme AA, Ercole PM, et al. Effect of reminder devices on medication adherence: The REMIND Randomized Clinical Trial. *JAMA Intern Med* 2017;177:624-631.

As Kronish and Moise noted in the editorial accompanying this article,[1] in the 1970s David Sackett, MD, and colleagues published groundbreaking work on medication compliance (as it was then called), revealing that only about half the hypertensive patients they studied were taking at least 80% of their medications.[2] Unfortunately, more than 40 years later, we still find that medication adherence is a major problem. As reported in the landmark World Health Organization report on medical therapy adherence, rates continue to hover around 50% adherence.[3] A recent systematic review and meta-analysis of 771 intervention trials found that there can be a nearly 30% improvement in adherence with intensive, face-to-face intervention.[4]

Choudhry et al sought to determine if a simple intervention (supplying non-adherent patients with reminder pill bottles) would increase medication adherence. Using a pharmacy benefits database, the researchers selected more than 50,000 patients for study, of which 36,739 were enrolled. To be eligible, patients must have been prescribed between one and three medications for at least one chronic illness, were on commercial insurance,

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and had filled between 30-80% of their prescriptions (nonadherence was defined as filling < 80% of prescriptions). Patients whose only chronic medication was an antidepressant were followed separately.

There were four arms of the study, three different "reminder bottles" and the control group, which continued to receive their medications in a plain pill bottle. The three study devices were a pill bottle with a toggle strip where each day could be slid over after the pill is taken, a pill bottle cap with a timer that shows the time since the bottle was last opened, and a standard plastic pill box with separate compartments for each day of the week. Patients were mailed the pill bottle devices with an enclosed card explaining how to use them. Patient records were collected for two years (February 2013-March 2015).

Perhaps the most surprising finding of the study, and not anticipated by the researchers, was that more than 15% of the patients in the control group (all "non-adherent" at baseline) became adherent to their medication prescriptions. The adherence rates ranged from 15.1-16.3% in the treatment arms, but all rates were statistically equal. The authors concluded that "no statistically significant difference in adherence was found between those in the control group and those who received a reminder device."

■ COMMENTARY

Before we reject the efficacy of simple pill bottle medication reminders, a few issues with this study must be addressed. As the authors admitted, since the devices were mailed to the patients with a card explaining how to use them, there is no way of knowing if the patients actually used the devices (or if they even received them). Furthermore, the large increase in adherence by the control group (more than 15% compared to the 2% adherence the researchers planned for) could obscure any benefit of the intervention. Lastly, using pharmacy data alone may have missed patients who had stopped taking their prescriptions on their doctors' orders (although this should have been even throughout the study arms).

While it's disappointing that this study did not find that a simple intervention of mailing non-adherent patients reminder pill bottles, it did show that patients can improve adherence significantly (all groups increased from 0% of patient adherence to approximately 15% adherence). Based on previous studies showing the benefits of face-to-face interventions, I will continue to discuss adherence with my patients and ask them if they think a reminder pill bottle with be helpful. ■

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ABSTRACT & COMMENTARY

Very Low-carbohydrate Ketogenic Diet May Reverse Type 2 Diabetes

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center; Clinical Professor, Keck School of Medicine, University of Southern California

Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: A very low-carbohydrate ketogenic diet demonstrated superiority to the plate method diet recommended by the American Diabetes Association for controlling and even reversing type 2 diabetes.

SOURCE: Saslow LR, Mason AE, Kim S, et al. An online intervention comparing a very low-carbohydrate ketogenic diet and lifestyle recommendations versus a plate method diet in overweight individuals with type 2 diabetes: A randomized controlled trial. *J Med Internet Res* 2017;19(2):e36. doi: 10.2196/jmir.5806.

This randomized, controlled trial conducted at the University of California, San Francisco compared a very low-carbohydrate ketogenic diet with the "create your plate" diet recommended by the American Diabetes Association for managing type 2 diabetes. Saslow et al previously conducted an in-person randomized, controlled trial;[1] the most recent study was conducted online. Both studies were small (25 patients) and showed the same results. HbA1c dropped more than twice as much with the very low-carbohydrate ketogenic diet compared to the plate method (average 0.8% vs. 0.3%). With an average HbA1c of 7.1% or 7.2% at baseline, more than half the very low carbohydrate subjects dropped their HbA1c to below 6.5%.

A very low-carbohydrate diet consisted of only 20-50 grams of nonfiber carbohydrates for ketones to appear in urine, reflecting fat metabolism. Patients in both groups were mailed diet plans. Patients in the very low-carbohydrate group were mailed urine test kits for ketones.

The only diabetes medication allowed by the study subjects was metformin, both before and during the trial. Patients were excluded if they had been on other medications. The trial lasted 32 weeks, with measurements made at 16 and 32 weeks. The very low-carbohydrate subjects also lost significantly more weight (12.7 kg vs. 3 kg) and significantly lowered their triglycerides (60.1 mg/dL vs. 6.2 mg/dL).

This study depended on careful patient selection and trusting subjects to report their nutrition accurately. The subjects were equally reliant online as in person, with similar results.

■ COMMENTARY

Type 2 diabetes reversal clinics are opening across the United States. Eric Westman MD, an internist at Duke University, is a pioneer of this therapy as part of the Duke Lifestyle Medicine Clinic he directs. Dr. Westman is a champion of the ketogenic diet, and has been part of research showing its superiority for managing diabetes.[2] Sarah Hallberg, MD, is an internist at Indiana University who reverses type 2 diabetes as part of a medically supervised weight loss program that relies on a very low-carbohydrate ketogenic diet. Dr. Hallberg started an online company, Virta Health, to help patients reverse their diabetes much the same way as is in this study.[3]

A very low-carbohydrate diet may be the natural human diet we consumed for the vast majority of our time as a species.[4] Eating only the foods of nature as primitive hunter-gatherers did turns out to be eating mostly fat and protein from nuts, seeds, coconut, avocado, meat (especially the organs), and fish. The carbohydrates in our "foods of nature" diet usually were around 10% of calories. The Inuit in the Artic and the Samburu and Maasai tribes in Africa do not consume any carbohydrates in their diet.[5]

When blood sugar is derived from fat and protein, the blood sugar level is steady throughout the day and night and serum insulin is very low.[6] It is becoming clear that insulin resistance, prediabetes, and type 2 diabetes are a stress response from eating excessive carbohydrates.

A ketogenic diet is gaining in popularity among the general population and among endurance athletes. Stephen Volek, RD, PhD, at The Ohio State University, has studied the ketogenic diet extensively, including its use among and effects on athletes.[7,8] Using fat for energy is time-honored and superior to fluctuating blood sugar levels that can occur by consuming so-called energy drinks and loading carbohydrates. It is time to rekindle Maimonides' admonition that "no disease that can be treated with diet should be treated by any other means." ■

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ABSTRACT & COMMENTARY

Treatment of Chronic Fatigue/Myalgic Encephalitis Syndrome

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Blockade of IL-1 activity with anakinra failed to reduce fatigue in patients with chronic fatigue syndrome.

SOURCE: Roerink ME, Bredie SJ, Heijnen M, et al. Cytokine inhibition in patients with chronic fatigue syndrome: A randomized trial. *Ann Intern Med* 2017 Mar 7. doi: 10.7326/M16-2391. [Epub ahead of print].

Roerink and colleagues at Radboud University Medical Center in Nijmegen randomized 50 females with chronic fatigue syndrome (CFS) to receive either a saline placebo or the interleukin-1 (IL-1) receptor antagonist anakinra. Each was given daily by subcutaneous injection for four weeks; the daily anakinra dose was 100 mg. The diagnosis of CFS was based on CDC criteria, and the primary outcome measure was the Checklist Individual Strength subscale (CIS-fatigue), a validated measure of fatigue severity at four weeks.

At four weeks, both the experimental and control groups demonstrated a reduction in CIS-fatigue score with no significant difference between them. Furthermore, while most patients remained severely fatigued, two (8%) anakinra recipients and five (20%) placebo recipients were no longer severely fatigued (i.e., they reached a level of fatigue considered within the normal range). Limiting the analysis to the 48% of patients who reported that their fatigue was triggered by an infection also did not detect a significant difference in CIS-fatigue score between treatment groups. There also was no significant difference in the following secondary outcomes at four weeks and 24 weeks: impairment, physical and social functioning, psychological distress, and pain severity.

Seventeen (68%) anakinra recipients experienced injection site reactions, as did one (4%) of the controls.

■ COMMENTARY

In 2015, the Institute of Medicine issued a report[1] that concluded that CFS is a biologically based illness and proposed a set of diagnostic criteria that differs from the CDC criteria used in the study reviewed here. They also proposed that the illness be called systemic exertion intolerance disease (SEID) rather than chronic fatigue syndrome/myalgic encephalitis (CFS/ME). Research into the cause or causes of this illness and its management have burgeoned since. The study by Roerink and colleagues was based on a number of observations suggesting that excess pro-inflammatory cytokine activity, perhaps within the central nervous system, was the underlying pathophysiology accounting for the reported symptoms.

Studies of cytokines in peripheral blood sometimes have produced contradictory results. This includes studies of IL-1, some of which have demonstrated elevated levels while others have not. It has been proposed that one reason for this is that the critical site of IL-1 production in causing the symptoms of CFS is not the peripheral blood but the central nervous system. In this regard, Roerink et al noted that anakinra can be detected in cerebrospinal fluid in low concentrations after intravenous or subcutaneous administration.

The placebo effect in this study was significant and similar to that seen in at least one other study. Of note is that the high frequency of injection site reactions associated with anakinra administration should have caused a bias favoring anakinra since it is likely that patients with such reactions may have assumed they were receiving an active drug, but this was not the case.

This study failed to identify benefit from anakinra administration in relief of the symptoms of CFS. The only therapies with demonstrated benefit to date are cognitive behavioral therapy and graded exercise, although patients may benefit from symptomatic therapies such as the administration of nonsteroidal anti-inflammatory agents for pain. ■

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ABSTRACT & COMMENTARY

Guillain-Barré Syndrome and Hepatitis E

By Michael Rubin, MD

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Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: Hepatitis E is the most common form of viral hepatitis worldwide and often is asymptomatic, but it is commonly associated with Guillain-Barré syndrome and Guillain-Barré variants.

SOURCE: Stevens O, Claeys KG, Poesen K, et al. Diagnostic challenges and clinical characteristics of hepatitis E virus-associated Guillain-Barré syndrome. *JAMA Neurol* 2017;74:26-33.

Antecedent infection initiating an immune response often is believed to result in Guillain-Barré syndrome (GBS), with prior infection of the gastrointestinal tract, most commonly by *Campylobacter jejuni*, or respiratory tract, noted in two-thirds. Other antecedent infections include human immunodeficiency virus (HIV), influenza, cytomegalovirus (CMV), and Epstein-Barr virus (EBV), and less commonly, varicella-zoster virus, herpes simplex virus, hepatitis A, B, C, and E viruses, *Haemophilus influenzae*, *Escherichia coli*, and *Mycoplasma pneumonia*. Zika virus recently has been identified as causally related to GBS. What is the prevalence and clinical spectrum of hepatitis E (HepE) virus-associated GBS and how may it be diagnosed accurately?

Undertaken at the Department of Neurology, University Hospital, Leuven, Belgium, this retrospective cohort study identified all GBS or GBS-variant patients who presented between Jan. 1, 2007, and Nov. 1, 2015, within four weeks of onset of neurological symptoms. Patients were categorized clinically as pure motor GBS, Miller-Fisher syndrome, Bickerstaff brainstem encephalitis, acute ataxic neuropathy, bifacial weakness with distal paresthesiae, acute multiple cranial neuropathies, pharyngeal-cervical-brachial variant, and overlap syndrome.

Clinical history and examination findings, results of lumbar puncture and blood work, including antiganglioside or anti-sulfatide antibodies (IgM and IgG against GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b, and sulfatides), and infectious serologic serum tests were reviewed. Patients accepted in transfer following intravenous immunoglobulin treatment and those without usable serum in the laboratory serum bank were excluded. Statistical analysis comprised the Shapiro-Wilk normality test and the two-tailed unpaired Mann-Whitney test, with $P < 0.05$ considered significant.

Among 88 patients with GBS or its variant, 73 satisfied inclusionary and exclusionary criteria, encompassing 44 men and 29 women, with mean age 52 years, of which 8% (n = 6) had positive IgM HepE assays, consistent with possible acute HepE infection, two of whom also tested positive for EBV or CMV. Elevated alanine aminotransferase (> 1.5 times the upper limit of normal) was found in four of these patients. Thus, 6% (n = 4) of this GBS cohort had probable acute HepE infection, two presenting with a GBS variant (acute ataxic neuropathy or the pharyngeal-cervical-brachial variant) and two others with classic GBS.

Of the two patients who tested positive for both HepE and CMV or EBV, one had mild predominantly sensory GBS and one had classic GBS. Acute HepE infection is associated with GBS, and elevated alanine aminotransferase may be a clue to its presence.

■ COMMENTARY

Hyper-endemic in many Asian and African developing countries, where infection is caused by HepE virus 1 and 2, and spread via the fecal-oral route through contaminated water, HepE also is endemic in developed countries, where HepE3 and HepE4 are the culprits, and are porcine zoonoses. Most often asymptomatic, HepE can cause acute and chronic hepatitis, and it is the most common cause of acute viral hepatitis worldwide.

HepE is associated with a variety of neurologic disorders, including GBS, which, in 2000, was reported as the first HepE-associated neurologic complication. Other disorders include neuralgic amyotrophy, encephalitis, meningitis, and myelitis. Mononeuritis multiplex often is reported with HepE, as well as a rare report of myositis.

Bell's palsy and vestibular neuronitis have occurred concomitantly with HepE, but a causal relationship remains speculative. Hepatitis is either absent or mild when seen in conjunction with neurologic complications of HepE. ■

PHARMACOLOGY UPDATE

Edaravone Injection (Radicava)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved edaravone, the first new treatment for amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) since the approval of riluzole more than 20 years ago. Edaravone is a potent radical scavenger that received orphan designation and was approved based on a clinical trial conducted in Japanese subjects. It will be marketed as Radicava.

INDICATIONS

Edaravone is indicated for the treatment of ALS.[1]

DOSAGE

The recommended initial treatment cycle is 60 mg given intravenously over 60 minutes daily for 14 days, followed by a 14-day drug-free period.[1] Subsequent cycles are daily dosing for 10 days of a 14-day cycle, followed by a 14-day drug-free period. Edaravone is available as a 30 mg/100 mL single-dose polypropylene bag.

POTENTIAL ADVANTAGES

Edaravone provides a new treatment option for ALS.

POTENTIAL DISADVANTAGES

The most common adverse reactions (vs. placebo) are contusion (15% vs. 9%), gait disturbance (13% vs. 9%), and headache (10% vs. 6%).[1] Hypersensitivity reactions, including cases of anaphylaxis, have been reported. The formulation contains sodium bisulfite, which may cause allergic-type reactions in susceptible individuals.[1] Edaravone does not appear to be effective in advanced ALS.[2] Long-term safety and effectiveness has not been established.

COMMENTS

Edaravone is a radical scavenger initially approved in Japan for treating acute cerebral embolism.[2] Its potential neuroprotective effect against oxidative stress in motor neurons led to its evaluation in ALS patients. The efficacy of edaravone was established in a six-month, randomized, placebo-controlled, double-blind study in Japanese subjects.[1] Patients were living independently and retained most activities of daily living, normal respiratory function, and had a disease duration of two years or less. Subjects were randomized to edaravone (n = 69) or placebo (n = 68). More than 90% of subjects were treated with riluzole. The primary efficacy endpoint was a comparison of the change between the two treatments in the ALS Functional Rating Scale, Revised (ALSFRS-R) total score from baseline to week 24. ALSFRS-R consists of 12 questions that evaluate fine and gross motor skills, bulbar, and respiratory function of patients, including speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs dyspnea, orthopnea, and respiratory insufficiency. Each question is scored from 0-4, with a higher score representing higher functionality. At week 24, changes were -5.01 ± 0.64 for edaravone and -7.50 ± 0.66 for placebo (difference, 2.49; 95% confidence interval, 0.99-3.98; $P = 0.0013$). The treatment effect of edaravone may be limited. An early confirmation study with a larger sample size (n = 206) that included subjects with longer disease duration (≤ 3 years vs. ≤ 2 years) and poorer respiratory function (FVC ≥ 70% vs. ≥ 80%) did not reach statistical significance.[2,4]

CLINICAL IMPLICATIONS

ALS is a rare, life-threatening, progressive neurodegenerative disease affecting upper and lower motor neurons with a mean survival of three to five years. Edaravone is the latest drug approved for ALS. It appears to show modest benefit in slowing disease decline in patients with short disease duration, good vital capacity, and concomitant use of riluzole. The cost for edaravone is estimated to be $1,303 per injection (60 mg) and is expected to be available in August.[5] Edaravone is under evaluation for acute ischemic stroke in several studies.[6] ■

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Clinical Briefs

By Louis Kuritzky, MD

Cardiovascular Consequences of Weight Gain

SOURCE: Bangalore S, et al. *N Engl J Med* 2017;376:1332-1340.

Obesity is recognized as an independent risk factor for numerous health consequences, including hypertension, cardiovascular events, cancer, and osteoarthritis. Whether progressive weight gain is associated with adverse outcome might be intuitively obvious, but has been less studied. The object of this report by Bangalore et al was to examine the association between weight variability and health outcomes, specifically addressing coronary heart disease.

The Treating to New Targets trial randomized patients with known coronary artery disease (n = 10,001) and a low-density lipoprotein reading of < 130 mg/dL to low-dose atorvastatin (10 mg/day) vs. high-dose (80 mg/day). In this post-hoc analysis, the authors examined the relationship between weight variability and subsequent coronary heart disease events over a mean five years' treatment.

For every 1.5-1.9 kg increase in body weight from baseline, the risk of incurring a coronary event increased by 4%. The increase in body weight in persons who were normal weight at enrollment was associated with a numerically greater (but not statistically significant) number of coronary events. However, persons who were overweight or obese exhibited marked increases in coronary events proportional to the degree of their weight gain. Clinicians should be vigilant to offer patients with coronary disease advice about optimal weight management. ■

Efficacy of Mandibular Advancement Devices vs. CPAP

SOURCE: Kuhn E, et al. *Chest* 2017;151:786-794.

Although there are "organic" rewards for the treatment of obstructive sleep apnea (OSA), such as blood pressure reduction in hypertensives, much of the benefit of intervention resides in the quality of life (QOL) category: less daytime fatigue, better concentration, less snoring, etc. Despite such favorable effects, short- and long-term compliance with continuous positive airway pressure (CPAP) often is difficult. How does the efficacy of mandibular advancement devices (MANDs) for QOL compare?

Kuhn et al performed a network metaanalysis of clinical trials (n = 23) that compared CPAP and/or MANDs to inactive control. The outcome of interest was QOL as assessed by the mental and physical components of the SF-36 score. Both CPAP and MANDs resulted in improved physical and mental segments of the SF-36 score, and there was no statistically significant difference between the two methods in efficacy.

MANDs often have been prescribed for patients with less severe OSA (mild-moderate), for patients who could not tolerate CPAP, or for persons for whom CPAP was not effective. These results suggest that MANDs are a viable alternative. The authors recommended that CPAP should remain the first-line treatment for most patients, perhaps because the studies employing MANDs have been restricted to less severe OSA cases. ■

Exercise-induced Rhabdomyolysis

SOURCE: Brogan M, et al. *Am J Med* 2017;130:484-487.

For exceptionally young clinicians who are unfamiliar with Mae West (1893-1980), she was an actress, playwright, comedian, and screenwriter credited with quotes such as, "When choosing between two evils, I always like to try the one I've never tried before," and, "Too much of a good thing is a really good thing." However, there are exceptions to all rules, right?

Sometimes, a segment of the population that decides to embrace exercise does too much of a good thing. Brogan et al enlightened us about 46 reported cases of acute rhabdomyolysis that occurred specifically after engaging in the vigorous activity of spinning: the use of stationary cycles that are adjustable for the degree of resistance and steepness of climb.

Even among physically fit women, a substantial amount of time above the ventilatory threshold (the level at which lactate begins to accumulate) is spent during a 45-minute spin class. Of the 46 above-mentioned cases of spin-class related rhabdomyolysis, 42 occurred after the first spinning class (in presumably less-conditioned individuals).

While clinicians endorse the health benefits of engaging in physical activity, patients who decide to choose spinning (cycling) as their exercise method must be cautioned to build exercise intensity gradually rather than doing too much of a good thing. ■

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CME QUESTIONS

1. **Approximately what percentage of patients are found to be adherent at least 80% of the time with chronic medications?**
   a. 10%
   b. 25%
   c. 50%
   d. 75%

2. **In a recent study, what type of diet demonstrated the ability to manage and even reverse type 2 diabetes?**
   a. A very low-carbohydrate ketogenic diet
   b. A diet recommended by the American Diabetes Association
   c. A balanced diet with calorie restriction
   d. None of the above

3. **Hepatitis E virus has been associated with which of the following neurological conditions?**
   a. Guillain-Barré syndrome
   b. Neuralgic amyotrophy
   c. Encephalitis
   d. Meningitis
   e. All the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Insomnia Disorder: Evidence for Psychological and Behavioral Interventions

Low Back Pain: Evidence for Nonpharmacologic Therapies