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ABSTRACT & COMMENTARY

## Timing of Protein Intake Does Not Influence Muscle Mass or Strength

*By Joseph Scherger, MD, MPH*

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

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

SYNOPSIS: The timing of protein intake during or between meals does not play a role in anabolic response, muscle strength, or functional outcomes.

SOURCE: Kim IY, et al. Protein intake distribution pattern does not affect anabolic response, lean body mass, muscle strength or function over 8 weeks in older adults: A randomized-controlled trial. *Clin Nutr* 2018;37:488-493.

A team of researchers at the University of Arkansas conducted studies on whether the timing of protein intake affects muscle strength, mass, or function. In another randomized, controlled trial conducted in 2015, Kim et al found no differences in the anabolic response to differing patterns of protein intake during a day, but the quantity and quality of protein were important.[1]

This 2018 study took place over an eight-week period to see if there were any anabolic differences based on protein timing. The authors found none. In a 2016 study, again conducted by these same investigators, similar results occurred in healthy young adults.[2] The sample size in this 2018 eight-week study was small — 14 adults randomized to two groups of seven. One group consumed most dietary protein with dinner, while the other group consumed dietary protein evenly throughout the day. Lean body mass, whole body protein kinetics, and muscle protein fractional synthesis rate were measured in both groups. The authors observed no differences.

### ■ COMMENTARY

Nutrition is a neglected area of medicine in the United States. However, when experts consider nutrition, recommendations often are too complicated to be practical. One such complexity, often used in adults

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relative to exercise, is the timing of protein intake. The work by Kim et al helps simplify nutrition recommendations. Protein intake is important, including the *quality* of the protein, but protein *timing* is of no value.

Racing to eat a high-protein bar or shake after exercise is not necessary. Keep adequate protein on hand, and good muscle mass and function will follow. ■

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## ABSTRACT & COMMENTARY

# Tailored Anticoagulation for Paroxysmal Atrial Fibrillation

***By Joshua D. Moss, MD***

*Associate Professor of Clinical Medicine, Cardiac Electrophysiology, Division of Cardiology, University of California, San Francisco*

**Dr. Moss reports he is a consultant for Biosense Webster and Abbott.**

SYNOPSIS: Intermittent anticoagulation guided by continuous assessment of arrhythmia status in patients with low-to-moderate risk did not result in any strokes or thromboembolic events over a relatively short follow-up period.

SOURCE: Waks JW, et al. Intermittent anticoagulation guided by continuous atrial fibrillation burden monitoring using dual chamber pacemakers and implantable cardioverter-defibrillators: Results from the Tailored Anticoagulation for Non-Continuous Atrial Fibrillation (TACTIC-AF) pilot study. *Heart Rhythm* 2018 Jul 5. pii: S1547-5271(18)30593-9. doi: 10.1016/j.hrthm.2018.06.027. [Epub ahead of print].

Anticoagulation with warfarin or direct oral anticoagulants (DOACs) for prevention of stroke and other thromboembolic events is a cornerstone of therapy for atrial fibrillation (AF). Whether AF is associated with symptoms, and regardless of episode duration and frequency, anticoagulation is recommended based on presence of risk factors such as age, hypertension, diabetes, and congestive heart failure. However, chronic anticoagulation therapy comes with the cost of elevated bleeding risk. Waks et al hypothesized that in patients with low arrhythmia burden and relatively low thromboembolic risk, the continuous monitoring afforded by modern implantable pacemakers and defibrillators could facilitate "tailored anticoagulation." Patients could start and stop anticoagulation based on AF burden, enabling protection from stroke and other thromboembolic events while reducing bleeding risks. This multicenter pilot study initially was designed as a randomized trial, with 1:1 assignment to standard therapy vs. tailored anticoagulation and 12 months follow-up. However, the control arm was removed after about two years to facilitate enrollment, and the trial continued as a single-arm prospective trial. Ultimately, 61 patients with a $CHADS_2$ score ≤ 3 and a St. Jude pacemaker or ICD with a functioning atrial lead and capability for remote monitoring were enrolled at 10 centers in the United States. Patients had to have experienced at least one episode of AF but a "low" overall burden: < 30 minutes of total AF per day, and no continuous episodes lasting > 6 minutes.

For 48 patients, tailored anticoagulation therapy was used. After one month of mandatory anticoagulation, their DOAC was discontinued if no significant AF burden was present. Anticoagulation was restarted if biweekly remote monitoring revealed an episode of continuous AF > 6 minutes or a total burden of > 6 hours over a 24-hour period. Automatic transmissions for AF also were programmed for atrial rates > 200 bpm lasting > 30 minutes, and for total AF burden > 6 hours over a 24-hour period. For 13 patients who remained in a control arm, anticoagulation was continued, regardless of AF burden. Patients in the tailored therapy

group averaged 71 years of age, 52% demonstrated a $CHADS_2$ score of 2 and 35% a $CHADS_2$ score of 1. During follow-up, these patients logged 3,763 total days on DOAC therapy after the first 30 days, out of 14,826 total monitored days. Due to protocol violations, 1,777 of those days on anticoagulation actually were "unnecessary." There were two gastrointestinal bleeds in patients on anticoagulation and one fatal intracranial hemorrhage in a patient not on anticoagulation at the time. No strokes or transient ischemic attacks (TIAs) occurred. There were two episodes of epistaxis in the smaller control group. The authors concluded that this approach could certainly improve patient compliance and decrease cost and bleeding risk compared with continuous DOAC therapy.

## ■ COMMENTARY

In many ways, anticoagulation for thromboembolic prophylaxis in patients with AF has become considerably easier with the advent of DOACs. With fewer dietary and drug interactions than warfarin and no need for regular monitoring of therapeutic levels, the threshold for physicians to prescribe the medications and patients to take them has decreased. Nevertheless, anticoagulation for AF remains underused, and the added expense of DOACs compared with warfarin can be an obstacle. Additionally, bleeding risks remain an important consideration. It is possible that a tailored approach to anticoagulation could reduce the risk of thromboembolic events in a select group of patients to the same degree as daily chronic anticoagulation, while simultaneously reducing both bleeding risks and costs. This pilot study represents an important step toward demonstrating the feasibility of such an approach. Although it was underpowered to detect thromboembolic events, with an average of only 309 days of follow-up per patient, the lack of any strokes or TIAs was reassuring. There also were very few adverse events and a dramatic reduction in the use of anticoagulation, despite protocol violations at one study site, which resulted in many days of unnecessary therapy.

The principal weaknesses of the study are the sample size, the limited follow-up, and the lack of a true control group. Additionally, patients were required to have an implanted pacemaker or defibrillator with an atrial lead and remote monitoring capabilities, which limits the population for which this approach is currently applicable. Other studies have demonstrated the use of an implantable loop recorder to assess AF burden. However, additional data will be needed to test whether the cost of invasive monitoring is offset by the savings on drug therapy, confirm whether thromboembolic risk is adequately addressed, and assess whether there are fewer bleeding events or improved quality of life with tailored therapy.

Additionally, some prior studies have shown strokes and TIAs can occur without an apparent temporal relationship to periods of AF, suggesting that other nonarrhythmic factors (such as left atrial size and/or function) may play a role. For now, the safest approach for paroxysmal AF in patients with stroke risk factors likely remains chronic, uninterrupted anticoagulation, particularly considering the relatively low rates of serious or fatal bleeding events in trials of DOACs. However, as further trials are conducted and additional safety data gathered, tailored therapy may eventually prove to be a viable or even superior alternative. ■

ABSTRACT & COMMENTARY

# Vitamin D and Glycemic Control in Patients With Type 2 Diabetes

***By Allison Becker, ND, LAc***

*Naturopathic Doctor, Acupuncturist in private practice, Evansville, WI*

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

SYNOPSIS: Findings from a meta-analysis show vitamin D supplementation was associated with improved glycemic control in vitamin D-deficient or non-obese patients with type 2 diabetes.

SOURCE: Wu C, et al. Vitamin D supplementation and glycemic control in type 2 diabetes patients: A systemic review and meta-analysis. *Metabolism* 2017;73:67-76.

The subject of vitamin D supplementation and its effects on various aspects of health is a popular topic. Previous studies have demonstrated the benefits of vitamin D extend past bone and parathyroid health to include metabolic diseases such as type 2 diabetes and obesity. Mechanisms of action on metabolism are elucidated further in the commentary. Researchers have found that lower vitamin D levels are relatively common in those with type 2 diabetes.[1,2] However, the causal relationship between vitamin D and type 2 diabetes is

unclear. Wu et al attempted to clarify this relationship through a careful meta-analysis and review of previous studies.

Currently, more than 400 million people worldwide suffer from diabetes.[3] Improving glycemic control is the primary goal in diabetes management. There are many effective dietary and pharmacological agents used in diabetes management. However, diabetes continues to rise at epidemic proportions. Gathering more tools to address this problem is wise. Other investigators have explored the use of vitamin D in glycemic control.[4] Some studies have shown benefit, while others have shown no benefit. Previous studies have included dietary intake of vitamin D, patients who did not have diabetes, and patients with prediabetes. Wu et al conducted this review and meta-analysis to evaluate an association between vitamin D supplementation, specifically, and the reduction of fasting blood glucose (FBG) as well as glycosylated hemoglobin A1c (HbA1c) only in patients with type 2 diabetes. FBG reflects daily glycemic fluctuations. HbA1c indicates the average plasma glucose level over the previous eight to 12 weeks.

Wu et al started with 637 articles and narrowed their list to include just 26 in the final analysis. They searched PubMed, Web of Science, and the Cochrane Library for articles published through March 2017 and included international publications in any language. The authors' numerous exclusions strengthened the final analysis. To be included in this review, studies had to be randomized, controlled trials of human subjects with type 2 diabetes that evaluated HbA1c and FBG. The studies used either vitamin D, vitamin D analogues, and/or vitamin D and calcium supplementation. The studies included also had to demonstrate some change in serum vitamin D and a difference between the intervention group and the control group. All 26 studies were printed in full-text articles.

Vitamin D deficiency was defined as serum 25(OH)D concentrations of < 20 ng/mL (50 nmol/L). Vitamin D insufficiency was defined as serum (OH)D concentrations of 20-30 ng/mL (50-75 nmol/L), and vitamin D sufficiency was defined as serum 25(OH)D concentrations of > 30 ng/mL (75 nmol/L). Other investigators have suggested that serum concentrations > 30 ng/mL maximize the noncalcemic benefits of vitamin D.[5]

Wu et al conducted a further analysis in subgroups including baseline 25(OH)D, body mass index (BMI), dosage of vitamin D supplementation, length of intervention, and change of 25(OH)D concentration. In this evaluation of moderating factors, Wu et al found vitamin D supplementation significantly benefitted FBG and HbA1c in those who were non-obese with a BMI < 30 kg/m$^2$. BMI is an attempt to quantify the amount of tissue mass, including muscle, fat, and bone, in an individual to categorize them as underweight, normal weight, overweight, or obese.

Another subgroup analysis showed that HbA1c and FBG levels both dropped significantly when changes in 25(OH)D serum levels were < 20 ng/mL or between 10-20 ng/mL. The connection between physiological parameters and serum vitamin D levels is important, demonstrating benefits even with small laboratory changes with vitamin D repletion. The dosing of vitamin D also was highly variable, from as low as 1,000 IU per day to a single intramuscular injection of 300,000 IU. Additionally, the course of intervention ran from four to 48 weeks. Because of this high variability in dosing quantity and trial length, this analysis failed to yield specific clinical recommendations. However, in patients who have a serum 25(OH)D level < 20 ng/mL and are non-obese, vitamin D supplementation can lower their glycemic parameters. Unfortunately, the authors did not identify a specific dosing schedule that can reach a beneficial serum level.

Although Wu et al were careful to streamline the data included in this analysis by excluding many other studies, there were some weaknesses in the methods to gather data. First, not all study authors reported hypoglycemic pharmacologic use. Authors of seven studies included in this analysis did not report diabetes pharmaceutical use; therefore, lower blood sugars could be attributed to pharmaceuticals rather than vitamin D supplementation. There was not a subgroup analysis conducted to eliminate this variable. Second, the numbers of participants in the included studies were relatively small. On average, studies included 30-40 participants. Third, most authors did not include the effects of sun exposure, dietary intake, or regular exercise, which all contribute to vitamin D synthesis.

Despite these limitations, we can conclude that patients with diabetes and deficient vitamin D levels would benefit from some amount of vitamin D supplementation. The exact amount and for how long has yet to be determined.

## ■ COMMENTARY

Previous studies regarding vitamin D and glycemic control have been conflicting and confusing. Some have demonstrated benefit, and others have found no benefit. No trials have shown a worsening of glycemic parameters with vitamin D supplementation. Most studies contained confounding variables and interfering factors that weaken their arguments in favor of or against vitamin D. Wu et al tried to resolve this confusion by presenting data from a highly selective group of studies, breaking the collected data into subgroups, and analyzing the data using different statistical methods. They focused specifically on vitamin D supplementation in people with type 2 diabetes and evaluated HbA1c and FBG as

their specific parameters. Most of the body's vitamin D is synthesized in the skin upon exposure to sunlight. Upon stimulation in the skin, vitamin D3 is produced from pro-hormone 7-dehydrocholesterol. Vitamin D3 (cholecalciferol) is the more bioactive form of vitamin D than vitamin D2 (ergocalciferol).[6] Vitamin D2 does not bind as well to receptors in human tissue as vitamin D3. Most experts agree vitamin D3 should be used in practice.[7] In this meta-analysis, Wu et al did not distinguish between the use of vitamins D3 and D2, and this discrepancy may contribute to a decreased metabolic effect overall.

To understand the mechanism of vitamin D, it is best to think of it more as a hormone than a vitamin. Instead of serving as a cofactor and facilitator for metabolic processes like a vitamin, vitamin D regulates metabolic processes.[8] The effect of vitamin D on glucose metabolism is not entirely clear. However, it is understood vitamin D deficiency impairs glucose-mediated insulin secretion in pancreatic beta cells.[9] Data suggest that normalization of vitamin D stimulates insulin secretion in rats that are deficient in vitamin D.[10] It is postulated vitamin D's glucose regulation occurs in two ways: by regulating plasma calcium levels, which regulate insulin synthesis and secretion, and through a direct action on pancreatic beta-cell function.[11]

In this meta-analysis, some studies included patients receiving insulin treatments, and serum insulin was not measured as a parameter. The specific effect of vitamin D supplementation on serum insulin is an area of research to be explored. Non-obese patients with diabetes received the most glycemic benefit from vitamin D supplementation in this meta-analysis. Although obesity is a risk factor for vitamin D deficiency,[12] these findings suggest improving vitamin D status in obese patients does not significantly improve their glycemic parameters. In one study, Hypponen et al reported that as BMI increased, serum 25(OH)D decreased and HbA1c increased,[13] suggesting the association between vitamin D and glucose metabolism might depend on body habitus. The most clinically relevant information in this analysis is to understand vitamin D as biologically active influence on metabolism. Further research on mechanism and specific clinical protocols has yet to be developed. However, in our non-obese patients with diabetes who are deficient in vitamin D, supplementing with vitamin D3 on a daily basis could yield glycemic benefits. ■

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ABSTRACT & COMMENTARY

# A Negative Nares Screen for MRSA Helps Exclude MRSA Pneumonia


***By Richard R. Watkins, MD, MS, FACP, FIDSA***

*Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH*



**Dr. Watkins reports that he has received research support from Allergan.**



SYNOPSIS: The authors of a meta-analysis determined that nares screening for methicillin-resistant *Staphylococcus aureus* (MRSA) has a high specificity and negative predictive value for MRSA pneumonia.

SOURCE: Parente DM, et al. The clinical utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening to rule out MRSA pneumonia: A diagnostic meta-analysis with antimicrobial stewardship implications. *Clin Infect Dis* 2018;67:1-7.

Although methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia is a serious illness associated with significant morbidity and mortality, its overall prevalence is low, especially as a cause of community-acquired pneumonia (CAP). Thus, clinicians frequently must deal with the dilemma of when to use empiric anti-MRSA therapy (e.g., vancomycin and linezolid), factoring in the inherent drawbacks, such as cost, adverse reactions, toxicities, and the promotion of antimicrobial resistance, associated with these agents.

To address this concern, Parente et al sought to determine the value of MRSA nasal screening in the management of MRSA pneumonia. They conducted a meta-analysis that included studies with information about both rates of positive MRSA nasal screening and the rates of MRSA pneumonia that were confirmed by culture.

All classes of pneumonia were included: CAP, hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), and ventilator-associated pneumonia (VAP). Studies that used MRSA surveillance cultures from sites other than the nares were excluded from the analysis. Researchers employed a bivariate random-effects model to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

There were 22 studies with 5,163 patients who met the inclusion criteria. Of these, 18 were retrospective, three were prospective, and one was not reported. The diagnostic criteria for MRSA pneumonia differed in the various studies, with most using radiographic, microbiological, and clinical criteria to determine the diagnosis. The MRSA nares surveillance method differed in the studies as well, with 11 using polymerase chain reaction (PCR), four using culture, and one using both methods. For the remaining six studies, the method was not described. The timing for obtaining MRSA screening was reported in 95.5% of studies.

For all pneumonia types, the sensitivity of MRSA nares screen to predict pneumonia was 70.9% (95% confidence interval [CI], 58.8-80.6%), specificity was 90.3% (95% CI, 86.1-93.3%), PPV was 44.8%, and NPV was 96.5%. For CAP and HCAP, the values were 85% sensitivity (95% CI, 59.7-95.6%), 92.1% specificity (95% CI, 81.5-96.9%), 56.8% PPV, and 98.1% NPV. For VAP, the values were somewhat different, with a sensitivity of 40.3% (95% CI, 17.4-68.4%), specificity of 93.7% (95% CI, 77.1-98.4%), PPV of 35%, and NPV of 94.8%. There was a low probability of publication bias as determined by funnel plot testing.

## ■ COMMENTARY

The overuse of vancomycin is a serious concern in clinical practice. The Parente et al study is welcome because it provides solid evidence that can help antibiotic stewardship efforts in reducing the amount of anti-MRSA antibiotics prescribed for pneumonia. Even though a positive MRSA screen was not diagnostic, if the screen result was negative, pneumonia could be ruled out in instances of CAP/HCAP.

The sensitivity and NPV were lower for VAP, which the authors blamed on artificial airways providing a secondary source of MRSA besides the nares. However, in the absence of risk factors for MRSA and the presence of a negative MRSA nasal screen, it seems reasonable to stop anti-MRSA therapy and then observe closely. Further clinical studies are needed to determine outcomes in patients with pneumonia whose therapy is modified based on the results of MRSA nasal screening.

There are some exceptions for which MRSA nasal screening might not be reliable to predict pneumonia. These include patients who were decolonized recently, those with a MRSA infection in the preceding 30 days, those with structural lung disease (such as cystic fibrosis or bronchiectasis), and those who are critically ill.

As with all meta-analyses, the strength of the findings is directly proportional to the robustness of the studies that are included. That said, 81.8% of the studies in the Parente et al meta-analysis featured a retrospective design, which makes them subject to confounding by indication and sampling bias. Moreover, verification bias is a concern because nasal screening results often influence culture collection and clinical diagnosis. It is notable that the confidence interval for the sensitivity associated with VAP was particularly wide (17.4-68.4%), which may reduce the value of this variable. Finally, not all the studies clearly defined the time that nasal swabs were collected compared to when the sputum cultures were taken.

The Parente et al meta-analysis has shown that a negative nasal screen for MRSA is a rapid, easy, and inexpensive way to exclude MRSA pneumonia. This will allow the discontinuation of anti-MRSA antibiotics to occur sooner, thus sparing patients unnecessary therapy and reducing costs. One potential strategy is to allow pharmacists to order MRSA nasal screens whenever a patient is prescribed vancomycin or linezolid for pneumonia. A negative result then could be discussed with the prescribing physician. Whether future pneumonia guidelines incorporate these new data remains to be seen. ■

PHARMACOLOGY UPDATE

# Cannabidiol Oral Solution (Epidiolex)

***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 a purified drug substance derived from marijuana for the treatment of two rare but severe forms of epilepsy in children. Cannabidiol (CBD) is a cannabinoid that does not share the psychoactive properties of tetrahydrocannabinol (THC). The product was granted priority review and received fast-track and orphan designations. It is marketed as an oral solution called Epidiolex.

## INDICATIONS

Epidiolex is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥ 2 years of age.[1]

## DOSAGE

The recommended starting dose is 2.5 mg/kg taken orally twice daily.[1] After one week, the dose can increase to 5 mg/kg twice daily. Based on response and tolerability, the dose may rise to a maximum of 10 mg/kg twice daily. Serum transaminases (ALT and AST) and total bilirubin levels should be determined prior to treatment initiation. Dosage adjustment is recommended in patients with moderate or severe hepatic impairment. A dose reduction should be considered with concomitant administration of a moderate or strong CYP3A4 or CYP2C19 inhibitor. A dose increase may be required with strong inducers of these isoenzymes. Epidiolex is available as an oral solution 100 mg/mL.

## POTENTIAL ADVANTAGES

The addition of CBD to conventional antiepileptics results in a significant reduction in the number of seizures in treatment-resistant patients with Lennox-Gastaut syndrome or Dravet syndrome.[1-4]

## POTENTIAL DISADVANTAGES

CBD is associated with dose-related elevation of serum transaminases (three times the upper limit of normal), somnolence/sedation, and weight loss (≥ 5%).[1] Other adverse reactions include decreased appetite, diarrhea, fatigue/malaise/asthenia, rash, and anemia. As with other antiepileptics, CBD may increase the risk of suicidal behavior and ideation.

## COMMENTS

The safety and efficacy of CBD were evaluated in three randomized, double-blind, placebo-controlled studies. Two included subjects with Lennox-Gastaut syndrome and one included subjects with Dravet syndrome.[1-4]

In the two studies that included Lennox-Gastaut subjects (n = 171 and n = 225), subjects were 2-55 years of age, previously inadequately controlled on a median of six antiepileptics, and on three concomitant antiepileptics at time of study entry, with or without vagal nerve stimulations and/or ketogenic diet.[1-3] Ninety-four percent of subjects in both studies were taking at least two antiepileptic drugs. The most common antiepileptics (> 30%) were clobazam, valproate, and levetiracetam. The primary efficacy outcome was the percent change from baseline in the frequency of drop seizures per 28 days over the 14-week treatment period. Secondary outcomes included the percent with a 50% reduction from baseline in drop-seizure frequency and Patient or Caregiver Global Impression of Change (S/CGIC) from baseline. Drop seizure was defined as an epileptic seizure involving the entire body, trunk, or head that leads to or could lead to a fall, injury, or slumping in a chair.[2] Median baseline frequency of drop seizures ranged from 71-87 per 28 days. These study authors used a two-week titration period followed by a 12-week maintenance period.

In study 1, subjects were randomized to CBD 20 mg/kg/day or placebo. In study 2, subjects were randomized to 10 mg/kg/day, 20 mg/kg/day, or placebo. In study 1, there was a median change at the 20 mg/kg/day dose of -44% (from a median baseline of 73.8 seizures/28 days) compared to -22% (median baseline of 71 seizures/28 days) for placebo. Forty-four percent demonstrated a ≥ 50% reduction in drop seizures compared to 24% for placebo. In study 2, median changes were -42%, -37%, and -17% for 20 mg/kg/day, 10 mg/kg/day, and placebo from baseline seizure frequencies of 86, 87, and 80, respectively. The percentage of subjects with ≥ 50% reduction in seizures were 39%, 36%, and 14%, respectively. In both studies, S/CGIC showed "slightly improved" compared to "no change" for placebo.

In the study of Dravet syndrome subjects with drug-resistant seizures (2-18 years of age), CBD 20 mg/kg/day reduced the median percentage of total convulsive seizures by 39% from a baseline of 12 convulsive seizures per 28 days. This was compared to 13% for placebo (baseline 15 seizures/28 days). The discontinuation rate

was 11.8% for the 20 mg/kg dose, 2.7% for the 10 mg/kg dose, and 1.3% for placebo.[1] The most common reason for discontinuation was elevation of serum transaminases. CBD does not appear to lead to abuse-related adverse events or cause physical dependence.[1]

## CLINICAL IMPLICATIONS

Lennox-Gastaut syndrome is a rare but severe form of epileptic encephalopathy with early childhood onset.[5,6] It is characterized by several seizure types and severe cognitive impairment. FDA-approved drugs to treat this syndrome include felbamate, topiramate, and clobazam. There are other drugs used off-label with limited success.[7] Dravet syndrome is a rare genetic form of epileptic encephalopathy associated with drug-resistant intractable seizures and high mortality. There are no FDA-approved drugs available to treat this syndrome.[6,8] Treatment commonly is initiated with valproate and benzodiazepines (e.g., clobazam) off label. CBD offers a significant option for these two severe forms of seizures that are generally multidrug-resistant. CBD is pending DEA rescheduling. The cost was not available at the time of this review. ■

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## CME QUESTIONS

**1. What is the optimal time to ingest protein relative to exercise during the day?**
a. In the morning with breakfast
b. Around noon
c. In the evening
d. Time does not matter

**2. A randomized trial of intermittent oral anticoagulants guided by device detected atrial fibrillation exhibited:**
a. no gastrointestinal bleeding.
b. no intracranial hemorrhage.
c. no strokes.
d. All of the above

**3. Which of these statements is *false* regarding vitamin D supplementation?**
a. Vitamin D supplementation benefits patients with diabetes who have a body mass index < 30 kg/m$^2$.
b. Vitamin D supplementation has no effect on glucose metabolism.
c. For patients with type 2 diabetes who are deficient in vitamin D, supplementing with vitamin D improves glycemic parameters.
d. Sufficient dosing of vitamin D and an optimal length of trial supplementation have not been determined because of this study.

**4. Which statement is correct?**
a. Detection of nasal MRSA has a positive predictive value > 90% for the diagnosis of MRSA pneumonia.
b. Detection of a nasal MRSA has a sensitivity > 95% for the diagnosis of MRSA pneumonia.
c. Failure to detect nasal MRSA has a negative predictive value > 95% for the diagnosis of MRSA pneumonia.
d. Failure to detect a nasal MRSA has no value in excluding the diagnosis of MRSA pneumonia.