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CANNABIS

ABSTRACT & COMMENTARY

Cannabis Use and Associated Health Conditions in Primary Care: An EHR Review

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

SYNOPSIS: This cross-sectional review of 185,565 patients' medical records found documentation of medicinal cannabis use in 2% of the records. Within this subgroup, 44.5% had documentation of one or more health conditions potentially benefitting from treatment with cannabis, 54.4% had documentation of one or more health conditions potentially worsening with cannabis use, and 36.6% had both types of health conditions.

SOURCE: Matson TE, Carrell DS, Bobb JF, et al. Prevalence of medical cannabis use and associated health conditions documented in electronic health records among primary care patients in Washington state. *JAMA Netw Open* 2021;4:e219375.

Cannabis now is legal for medicinal use in more than half of U.S. states. Although multiple factors, including federal restrictions on cannabis research, have hindered the development of practical, evidence-based guidelines regarding cannabis, this agent is gaining traction for nonmedicinal purposes in the United States as well, with 18 states currently allowing such use among adults.[1,2]

Despite state legislation, cannabis is illegal on a federal level. According to the Centers for Disease Control and Prevention, cannabis held the dubious honor of being the most commonly used federally illegal substance in the United States in 2019, with an estimated 48.2 million individuals reporting use during that year.[3]

Recognizing that "cannabis use is highly relevant to a patient's care," Matson et al conducted a descriptive, cross-sectional study of electronic health record (EHRs) in a large health system (Kaiser Permanente) to determine the prevalence of documented medicinal cannabis and diagnoses associated with these

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Summary Points

- This cross-sectional, electronic health record review of 185,565 patients in Washington (where recreational cannabis has been legal for adults since 2012 and medicinal cannabis has been legal since 1998) drew data from 25 Kaiser Permanente medical clinics, where all primary care patients are screened annually for cannabis use.
- The goal of the study was to find the prevalence of documentation of medicinal cannabis use and associated health conditions in this population.
- Results included medicinal cannabis use in 3,551 patients (2%), nonmedicinal cannabis use in 36,599 patients (20%), and no cannabis use documented in 145,415 patients (78%).
- Among the population with documented medicinal cannabis use, there was a higher prevalence of health conditions for which cannabis could both be helpful and convey risk when compared to the patients with documented nonmedicinal cannabis use or no cannabis use.

patients from Nov. 1, 2017, until Oct. 31, 2018. This investigation took place across 25 primary care clinics in Washington, where medicinal cannabis has been legal since 1998 and recreational cannabis was approved in 2012. All primary care patients are screened annually for cannabis use as part of a routine seven-item behavioral health screen by responding to the question "How often in the past year have you used marijuana?"

However, this screening question does not differentiate medicinal from nonmedicinal cannabis use. To do so, Matson et al employed a natural language processing (NLP) program (a type of artificial intelligence) to find references to medicinal cannabis use in the EHRs within a specified time before and after the appointment.[4] To help eliminate bias in reporting, employees of the health system were excluded from the study.

Matson et al used a 2017 comprehensive review of the health effects of cannabis by The National Academies of Science, Engineering, and Medicine (NASEM) to categorize health conditions into one of three sectors: potential benefit from cannabis, potential risk from cannabis, and inconclusive evidence.[5]

Out of the 185,565 patient charts screened during a primary care visit, 3,551 (2%) had documentation of medicinal cannabis use, 36,599 (20%) documented cannabis use without mention of medicinal use, and 145,415 (78%) did not document cannabis use during the past year. Out of the 40,150 patients documenting cannabis use of any sort, 9% of the charts reflected medicinal cannabis use. Based largely on observational studies, NASEM identified at least five conditions for which cannabis has potential benefits: chronic noncancer pain, multiple sclerosis, muscle spasms or spasticity, severe nausea, and sleep disorder.[5]

After analyzing the study cohort, including adjustment for demographic and socioeconomic factors, Matson et al found patients with EHR-recorded medicinal cannabis use had a higher prevalence of one or more of these conditions when compared with members of the other two groups (nonmedicinal or nonusers of cannabis). Overall, 49.8% of the medicinal use group had at least one of these diagnoses documented compared with 39.9% of the patients with documented nonmedicinal cannabis use and 40% of the patients with no documented cannabis use. (*See Table 1.*)

However, patients with documented medicinal cannabis use also had a higher prevalence of NASEM-identified health conditions potentially exacerbated or worsened by cannabis use, again adjusted for the demographic and socioeconomic covariates, when compared with patients in the other two groups. These conditions

included serious mental illness (e.g., schizophrenia and bipolar), depression, substance use disorder, and respiratory conditions.[5] (*See Table 2.*)

The adjusted prevalence of health conditions for which there is inconclusive evidence for cannabis use varied across the subgroups. For example, the prevalence of eating disorders, hypertension, cancer, and heart disease did not significantly vary with documentation of cannabis use. The prevalence of anxiety was higher in the medicinal cannabis group (28.7%) compared to 18.5% in the nonmedicinal cannabis group and 13.2% in noncannabis users, while heart disease (13.4%) was slightly higher in the noncannabis users than either of the cannabis-user groups (11% to 11.9%).

When compared with the two other groups, the medicinal cannabis group had the highest prevalence of patients with health conditions that potentially can benefit from cannabis as well as conditions for which cannabis use poses risk. Specifically, the medical cannabis group prevalence for these conditions was 33.6% compared with 25.2% in the nonmedicinal cannabis group and 22.3% in the noncannabis users.

■ COMMENTARY

Matson et al present a unique, large-scale record review quantifying a 2% provider documentation of medical cannabis use among 185,565 patients and an additional 20% patient-documented cannabis use (without documentation of medicinal use.) Although it certainly is possible that use in any category is underreported, this study is meant to reflect provider and patient documentation and responses. One caveat noted by Matson et al is that, since the medicinal documentation was extracted via a NLP program, it is possible that error could have contributed more to the medicinal cannabis numbers as opposed to the nonmedicinal cannabis group, whose quantification was based on direct responses to a questionnaire.
It is important to reiterate that this study is purely observational — there is no evidence or attempt to understand cause and effect, therapeutic benefits, or risks from use of cannabis, or motivation for cannabis use. These remain important areas for further

Table 1. Adjusted Prevalence of Health Conditions Potentially Benefitting from Cannabis Use

	Documentation of Cannabis for Medicinal Use (n = 3,551)	Documentation of Nonmedicinal Cannabis Use (n = 36,599)	Documentation of No Cannabis Use (n = 145,415)
Chronic noncancer pain	35.4 (95% confidence interval [CI], 34.1-36.7)	28.3 (95% CI, 27.8-28.7)	28.3 (95% CI, 27.8-28.7)
Multiple sclerosis	0.6 (95% CI, 0.4-0.8)	0.4 (95% CI, 0.3-0.5)	0.3 (95% CI, 0.3-0.4)
Sleep disorder	21.8 (95% CI, 20.6-22.9)	18.1 (95% CI, 17.7-18.5)	18.5 (95% CI, 18.3-18.6)
Muscle spasms/spasticity	5.1 (95% CI, 4.5-5.7)	3.5 (95% CI, 3.3-3.7)	3.5 (95% CI, 3.4-3.6)
Severe nausea	7.6 (95% CI, 6.9-8.2)	4.8 (95% CI, 4.6-5.1)	4.3 (95% CI, 4.2-4.4)
Any condition potentially benefitting from cannabis use	49.8 (95% CI, 48.3-51.3)	39.9 (95% CI, 39.4-40.3)	40.0 (95% CI, 39.8-40.2)

Table 2. Adjusted Prevalence of Health Conditions Potentially at Risk from Cannabis Use

	Documentation of Cannabis for Medicinal Use (n = 3,551)	Documentation of Nonmedicinal Cannabis Use (n = 36,599)	Documentation of No Cannabis Use (n = 145,415)
Serious mental illness	2.8 (95% confidence interval [CI], 2.0-3.2)	2.0 (95% CI, 1.9-2.1)	1.3 (95% CI, 1.2-1.3)
Chronic obstructive pulmonary disease	15.6 (95% CI, 14.6-16.6)	15.3 (95% CI, 14.9-15.7)	14.7 (95% CI, 14.5-14.8)
Substance use disorder	21.9 (95% CI, 20.6-23.1)	14.1 (95% CI, 13.7-14.5)	7.1 (95% CI, 7.0-7.3)
Opioid overdose	0.2 (95% CI, 0.1-0.3)	0.2 (95% CI, 0.1-0.2)	0.1 (95% CI, 0.1-0.1)
Any condition for which cannabis has potential risk	60.7 (95% CI, 59.0-62.3)	50.5 (95% CI, 50.0-51.0)	42.7 (95% CI, 42.4-42.9)

investigation to describe the relative benefits and risks of cannabis use more fully. Further results from this record review reveal that patients with documented medicinal cannabis use in this investigation have a higher prevalence of health conditions potentially benefiting and potentially harmed by cannabis when compared with patients in the other groups. This sparks a valuable takeaway message for primary care providers — be cognizant of asking patients about medicinal and other cannabis use, and review potential risks and benefits.

Unfortunately, there currently is limited (but growing) evidence of the potential risks and benefits for cannabis use with any of the specified conditions. There is evidence of cannabis' efficacy in treating chronic pain in adults, in symptoms of spasticity in multiple sclerosis, and short-term improvement for insomnia. There is established efficacy for using cannabinoids in treating chemotherapy-induced nausea and vomiting in adults. As more studies are completed, knowledge about dose, interactions, targeted demographic groups and contraindications likely will increase, allowing for the development of treatment guidelines and more widespread use. There is evidence that repeated cannabis use is associated with developing cannabis use disorders and that this risk is higher when cannabis use begins in the early teen years. There is moderate evidence suggesting an association between cannabis use and substance use disorder (alcohol and illicit drugs). There is evidence that cannabis use increases the risk of developing schizophrenia, other psychotic disorders, and social anxiety disorder, and limited evidence of an association with depression. While there is evidence that smoked forms of this agent may worsen pulmonary conditions, this appears reversible when cannabis use is stopped. However, the specifics of these and other risks remain uncharacterized.[6,7]

This study can serve as a reminder for the integrative provider to screen patients for cannabis use and use this as an opportunity to share what is known and unknown about potential risks and benefits. It is often tempting to ignore what we do not understand — this clearly is not a productive path to take in medicine and can hinder efforts to develop full knowledge of a field. While there is a great deal of ambiguity in discussing cannabis use risks and benefits, offering patients information about what is known and identifying and documenting medicinal and nonmedicinal use are valuable first steps on the way to gain a more comprehensive overview of the field. ■

REFERENCES

1. National Conference of State Legislatures. State medical marijuana laws. Published Aug. 23, 2021. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx
2. Yu B, Chen X, Chen X, Yan H. Marijuana legalization and historical trends in marijuana use among U.S. residents aged 12-25: Results from the 1979–2016 National Survey on drug use and health. *BMC Public Health* 2020;20:156.
3. Centers for Disease Control and Prevention. Marijuana and public health: Data and statistics. Updated June 8, 2021. https://www.cdc.gov/marijuana/data-statistics.htm
4. Yse DL. Your guide to natural language processing (NLP). *Towards Data Science*. Published Jan. 15, 2019. https://towardsdatascience.com/your-guide-to-natural-language-processing-nlp-48ea2511f6e1
5. Committee of the Health Effects of Marijuana. Health effects of marijuana and cannabis-derived products presented in new report. *The National Academies of Sciences, Engineering, and Medicine*. Published Jan. 12, 2017. https://www.nationalacademies.org/news/2017/01/health-effects-of-marijuana-and-cannabis-derived-products-presented-in-new-report
6. Hall W. A summary of reviews of evidence on the efficacy and safety of medical use of cannabis and cannabinoids. *European Monitoring Centre for Drugs and Drug Addiction*. Published December 2018. https://www.emcdda.europa.eu/system/files/publications/12852/Medical-Cannabis-BackgroundPaper.pdf
7. National Institute on Drug Abuse. Marijuana research report: Is marijuana safe and effective as medicine? Published July 2020. https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-safe-effective-medicine

SLEEP

ABSTRACT & COMMENTARY

Rapid Eye Movement Sleep Duration Is Predictive of Life Expectancy

By Alan Z. Segal, MD

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SYNOPSIS: Total sleep duration declines with increasing age, as does the fraction of sleep spent in rapid eye movement (REM) sleep. The decline in REM is associated with increasing mortality, but it is not clear if this is a cause or a marker of declining health and declining brain function.

SOURCE: Leary EB, Watson KT, Ancoli-Israel S, et al. Association of rapid eye movement sleep with mortality in middle-aged and older adults. *JAMA Neurol* 2020;77:1241.

Summary Points

- The Outcomes of Sleep Disorders in Older Men (MrOS) and the Wisconsin Sleep Cohort (WSC) both are showing a rising degree of mortality over time and, therefore, increasingly are capable of providing insight into the measure of rapid eye movement sleep and mortality.
- MrOS enrolled 2,675 subjects, all men, and generally older (mean age of 76 years at enrollment between 2003 and 2005). Overall, 52% of the MrOS cohort has died. WSC, with a total of 1,386 subjects, enrolled men and women roughly equally and had a mean age of 51 years at enrollment in 1998.
- Both studies showed a relationship between REM sleep and longevity. MrOS showed a 13% increase in mortality for every 5% reduction in REM sleep. Men achieving < 15% REM sleep showed a mortality hazard ratio (HR) of 1.35 compared to those who spent > 15% of their sleep in REM.

Although the precise physiological benefit of sleep remains poorly understood, lack of sleep has multiple consequences, including cardiovascular disease, depression, impairments in cognition, and overall mortality. Much of sleep research uses subjects' self-reporting of sleep duration and quality, but cannot address details, such as sleep stages, e.g., differentiating between rapid eye movement (REM) and non-REM (NREM) sleep. Although wearable technologies (such as Fitbit, Whoop, or Apple Watch) increasingly are capable of using accelerometry and pulse oximetry monitoring to accurately identify sleep stages, polysomnography remains the gold standard in quantification of REM and NREM (stages 1, 2, or 3) sleep.

The two large, prospective cohorts studied here gathered valuable comprehensive polysomnography data and can be considered among the "Framingham Studies" of sleep research. Now approximately 20 years old, the Outcomes of Sleep Disorders in Older Men (MrOS) and the Wisconsin Sleep Cohort (WSC) both are showing a rising degree of mortality over time and, therefore, increasingly are capable of providing insight into this crucial outcome measure. There are important differences between MrOS and WSC. MrOS enrolled 2,675 subjects, all men, and generally older (mean age of 76 years at enrollment between 2003 and 2005). Overall, 52% of the MrOS cohort has died. In contrast, WSC, with a total of 1,386 subjects, enrolled men and women roughly equally and had a mean age of 51 years at enrollment in 1998. Both studies showed a relationship between REM sleep and longevity. MrOS showed a 13% increase in mortality for every 5% reduction in REM sleep. Men achieving < 15% REM sleep showed a mortality hazard ratio (HR) of 1.35 compared to those who spent > 15% of their sleep in REM.

WSC had a longer period of follow up (on average, 20 years compared to 12 years in MrOS), but overall mortality was only 13%, given that it studied younger patients. WSC showed a 1.17 HR of death among those with < 15% of the night in REM sleep. Additionally, both studies showed that the mortality benefit was specifically the result of REM duration rather than overall sleep quantity. Results were comparable whether subjects slept for shorter (five- to seven-hour) compared to longer (six- to eight-hour) periods. REM duration ranged from 0% to 44% (19% on average) in MrOS and 0% to 43% (18% on average) in WSC. All of these data were statistically significant, controlling for covariables, such as race/ethnicity, educational level, body mass index, hypertension, smoking status, alcohol, caffeine, and use of sleep aids.

■ COMMENTARY

The results reported here were similarly shown in the Sleep Heart Health Study (SHHS), a large cohort study of 6,600 subjects with obstructive sleep apnea (OSA).[1] However, in SHHS, the benefit of REM sleep was found only in women, likely because of the overwhelmingly deleterious effect of OSA among male subjects. Other studies of REM vs. NREM sleep have cast doubt on the specificity of REM as a marker of effective sleep.

Although some have shown benefits of REM for cognitive performance and mood, others suggest that total sleep time, or quantity of slow wave (stage 3) sleep rather than REM, seemed more favorable in the prevention of obesity and metabolic syndrome. As the authors observed, the results reported here are generalizable, given that they were replicated in two well-validated cohorts, diverse in gender and age. They also pointed out obvious weaknesses, including that both studies were more than 90% of white ethnicity. The authors also acknowledged one of the thorniest issues in this type of sleep research — that is, reverse causality. It remains unknown whether REM sleep merely is a marker of brain and overall physical health, rather than a direct cause of longevity. ■

REFERENCE
1. Butler MP, Emch JT, Rueschman M, et al. Apnea-hypopnea event duration predicts mortality in men and women in the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2019;99:903-912.

COVID-19

ABSTRACT & COMMENTARY

Vitamin D and COVID-19

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN; Department of Pediatrics, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates

SYNOPSIS: Low levels of vitamin D are associated with in-hospital mortality in patients with COVID-19, but causality is not yet known.

SOURCE: Angelidi AM, Belanger MJ, Lorinsky MK, et al. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: A cohort of COVID-19 hospitalized patients. *Mayo Clin Proc* 2021;96:875-886.

Vitamin D has immunomodulatory properties as well as anti-inflammatory activity. In fact, vitamin D deficiency has been associated with both an elevated risk of acute respiratory infection and worse clinical outcomes following critical illnesses. Vitamin D deficiency also is associated with problems, such as obesity, older age, and cardiac disease, that are risk factors for bad outcomes with COVID-19. Thus, investigators have wondered if vitamin D deficiency (and potential treatment) might influence the clinical course of COVID-19.

Angelidi and colleagues performed a retrospective study of adults who were hospitalized at one of two hospitals (one in Boston and one in New York) with COVID-19 from February to mid-May 2020. They reviewed records and compared patient data to 25-hydroxyvitamin D levels determined either at the time of hospital admission or within the preceding six months.

A total of 144 patients were included in the study: 79 with vitamin D levels of less than 30 ng/mL and 65 with levels of 30 ng/mL or higher. The median age was 66 years. Overall, 44% of subjects were male, and 42% were non-Hispanic Blacks. The median body mass index was 29. More than 90% of included individuals had at least one significant medical comorbidity, with hypertension (74%), hyperlipidemia (55%), and diabetes (44%) being especially common. Cough, dyspnea, fever, and/or malaise were presenting symptoms in most of the patients.

Steroids were used in the management of 24% of patients, antivirals were used in 10%, an antibiotic (usually azithromycin) was used in 72%, and hydroxychloroquine was used in 44%. Treatment included oxygen in 64% of patients and mechanical ventilation in 27%; 39% of patients required intensive care. In-hospital mortality was 18%.

Mortality was higher (25% vs. 9%) in patients with low (< 30 ng/mL) vs. higher 25-hydroxyvitamin D levels. The timing (during the six months prior to admission vs. during the hospitalization) of vitamin D testing was not related to mortality. Of dozens of variables, only vitamin D level, age, malignancy, and chronic obstructive pulmonary disease were associated with an increased risk of in-hospital death with COVID-19. Doing careful statistical analysis, researchers found hypovitaminosis D was strongly associated with in-hospital mortality, even independent of medical comorbidities. The inverse association between vitamin D level and mortality was present whether 20 ng/mL or 30 ng/mL was used as the cutoff (thus, whether there was vitamin D deficiency or insufficiency).

■ COMMENTARY

Angelidi and colleagues carefully and convincingly showed that low vitamin D levels are associated with mortality in patients hospitalized with COVID-19. Of course, this association does not necessarily imply causality, and it does not prove that either preventive or therapeutic vitamin D administration would alter mortality. Low vitamin D levels have been associated previously with other factors that give risk for poor outcomes with COVID-19, including obesity and diabetes. However, in Angelidi's careful analysis, low vitamin D levels were independently associated with in-hospital mortality from COVID-19. There likely is either a causal effect of hypovitaminosis on the course of COVID-19 or there are other unmeasured variables, such as outdoor activity, that link both hypovitaminosis D and death from COVID without the vitamin D level directly affecting the course of COVID-19.

Hypovitaminosis D does seem causally related to other respiratory infections, even if a causal link has

Summary Points

- This study investigated the safety and efficacy of cannabidiol in treating focal seizures associated with tuberous sclerosis complex (TSC), an autosomal dominant disorder caused by sequence variations in the TSC1 and/or TSC2 genes.
- Overall, 16.9% of patients taking CBD had a 75% reduction in seizure frequency vs. none in the placebo group.

yet to be proven for COVID-19. Low vitamin D levels are seen more commonly in patients with acute respiratory infection than in healthy controls, and vitamin D does have an effect on immune functioning.[1] However, studies of vitamin D supplementation to prevent respiratory infections have yielded mixed results.[1] A new meta-analysis of studies of vitamin D as prevention for acute respiratory infection in children aged 1 to 15 years showed a significant (P = 0.018) but modest (odds ratio, 0.92, with 95% confidence interval, 0.86 to 0.99) effect when supplements of 400 IU/day to 1,000 IU/day were administered for up to 12 months.[1]

It is important to consider the timing of effects of intervention. Whether vitamin D provides protection against acquiring SARS-CoV-2 or other respiratory pathogens, different mechanisms of action could be necessary for vitamin D to be effective therapeutically. Recently, Griffin and colleagues summarized the various stages of COVID-19 and eloquently reviewed potential effects of various interventions at various times before, during, and after the actual infection.[2]

A recent placebo-controlled study of high-dose vitamin D as treatment of established COVID-19 infection included 236 hospitalized adults in multiple centers in Brazil (mean age 56 years, mean 25-hydroxyvitamin D level 21 ng/mL at entry into the study, with 20 ng/mL being the upper limit of "deficiency").[3] Vitamin D levels increased significantly with treatment, and no significant adverse events were noted.[3] However, hospital length-of-stay, need for intensive care, need for mechanical ventilation, and mortality were not altered by vitamin D treatment.[3]

Thus, these new data remind us that hypovitaminosis D is at least associated with respiratory infections, but that preventive supplementation only modestly reduces the risk of acquiring infection (in children for non-COVID-19 infection), and therapeutic administration of vitamin D does not alter the course of

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adults being hospitalized with COVID-19. Vitamin D generally is safe in the preventive and therapeutic doses used, but further convincing data will be required before vitamin D is recommended to either prevent or treat COVID-19.

Two years ago, Hu and colleagues reported that patients with chronic hepatitis B had lower vitamin D levels than did healthy controls, and among hepatitis B patients, viral loads were inversely correlated with vitamin D level.[4] Vitamin D also has been proposed for the prevention and treatment of a variety of other conditions, including diabetes, multiple sclerosis, and cognitive decline. Observational studies are supportive, but systematic reviews and randomized controlled trials are lacking.[5]

Although it seems reasonable to supplement individuals with or at risk of hypovitaminosis D to maintain a "normal" vitamin D level, definitive studies do not yet support widespread recommendations to use vitamin D specifically to prevent or treat these other conditions.[5,6] ■

REFERENCES

1. Jolliffe DA, Camargo CA Jr, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: A systematic review and meta-analysis of aggregate data from randomized controlled trials. *Lancet Diabetes Endocrinol* 2021; doi 10.1016/S2213-8587(21)00051-6.
2. Griffin DO, Brennan-Rieder D, Ngo B, et al. The importance of understanding the stages of COVID-19 in treatment and trials. *AIDS Rev* 2021;22:40-47.
3. Murai IH, Fernandes AL, Sales LP, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: A randomized clinical trial. *JAMA* 2021;325:1053-1060.
4. Hu Y-C, Wang W-W, Jiang W-Y, et al. Low vitamin D levels are associated with high viral loads in patients with chronic hepatitis B: A systematic review and meta-analysis. *BMC Gastroenterol* 2019;19:84.
5. Maretzke F, Bechthold A, Egert S, et al. Role of vitamin D in preventing and treating selected extraskeletal diseases — an umbrella review. *Nutrients* 2020;12:969.
6. Thacher TD. Vitamin D and COVID-19. *Mayo Clin Proc* 2021;96:838-840.

CME QUESTIONS

1. Matson et al reviewed medical records of primary care patients looking for prevalence of documentation of cannabis use and found that:
a. more than 50% of the clinicians neither asked nor recorded information about cannabis use, but almost 85% documented information about alcohol use.
b. medical cannabis use was documented in 2% of the 185,565 patients, and nonmedical use was documented in another 20%.
c. a sampling of urine drug screens among the population revealed that about 22% of the 185,565 patients had results indicating current cannabis use.
d. patients using medical cannabis had a higher prevalence of health conditions for which cannabis may be effective and a lower prevalence of health conditions that may be worsened by using cannabis when compared with the nonmedical and nonusers of cannabis.

2. Which of the following statements about rapid eye movement (REM) sleep is true?
a. REM sleep duration has no physical consequences.
b. Sleep apnea does not alter REM sleep duration.
c. Reduction in REM duration is associated with increased mortality.
d. REM sleep does not occur in older people > age 65 years.

3. Vitamin D administration has proven effectiveness in:
a. preventing respiratory infections in children.
b. treating COVID-19 in adults.
c. treating chronic hepatitis B.
d. preventing multiple sclerosis.

[IN FUTURE ISSUES]

Yoga Breathing for COVID

Fish Consumption and Cardiovascular Health

High-Dose Electronic Media Use in 5-Year-Olds