

# Internal Medicine

## [ALERT]

Evidence-based summaries of the latest research in internal medicine

### ABSTRACT & COMMENTARY

## Poor Diet May Cause More Than 80,000 Cancers Each Year in the United States

By Joseph E. Scherger, MD, MPH

Core Faculty, Eisenhower Health Family Medicine Residency Program, Eisenhower Health Center, La Quinta, CA;  
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:** In a recent analysis, investigators noted a correlation between a diet loaded with processed red meat and various types of cancers.

**SOURCE:** Zhang FF, Cudhea F, Shan Z, et al. Preventable cancer burden associated with poor diet in the United States. *JNCI Cancer Spectrum*. Published May 22, 2019. Available at: <http://bit.ly/2XnfALL>. Accessed June 20, 2019.

A team from the Friedman School of Nutrition Science and Policy at Tufts University used some databases from multiple sources to conduct a comparative risk assessment of diet and cancer in the United States. Zhang et al found an estimated 80,110 new cancer cases attributable to a suboptimal diet. A total of 67,488 of these were direct dietary associations and 12,589 were obesity-mediated associations. Colorectal cancer accounted for both the highest number of new cancer cases (52,225) and the highest proportion of cases (38.3%). Other cancers associated with a poor diet were cancers of the mouth, pharynx, and larynx (14,421) as well as endometrial (3,165), breast (3,059), kidney (2,017), stomach (1,564), liver

(1,000), pancreatic (538), and esophagus (475). The authors noted that a high intake of processed meat carried the highest association with these cancers. A low consumption of whole grains and dairy also increased the risk. The authors did not study food that might prevent cancer, such as a plant-based diet.

### ■ COMMENTARY

This study adds to growing evidence showing that the modern industrial diet leads to a heavy cancer burden. In 2010, an oncology fellow named Siddhartha Mukherjee published *The Emperor of All Maladies: A Biography of Cancer*.<sup>1</sup> In it, he reported that early in human history, cancer was a rare disease. However, over

**Financial Disclosure:** Internal Medicine Alert's Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott, Acadia, Allergan, AstraZeneca, Avadel, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mylan, and Salix; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Editorial Group Manager Leslie Coplin; and Accreditations Manager Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

### [INSIDE]

Workplace Bullying and Violence

page 98

The Return of Measles

page 99

Statin Use and Dementia

page 101

Pharmacology Update: Emgality

page 102

**Internal Medicine Alert** (ISSN 0195-315X) is published semi-monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

© 2019 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

**SUBSCRIBER INFORMATION**  
(800) 688-2421  
customerservice@reliasmedia.com  
[ReliasMedia.com](http://ReliasMedia.com)

**Subscription Prices**  
United States:  
Print: 1 year with free AMA PRA Category I Credits™: \$349  
Add \$19.99 for shipping & handling.

Online only: 1 year (Single user) with free AMA PRA Category I Credits™: \$299

**Back issues: \$21.** Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and \$30 shipping.  
Elsewhere: Add \$30 shipping.

**ACCREDITATION**  
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designs this enduring material for a maximum of 2 AMA PRA Category I Credit(s)™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 1/15/2019. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 2 AAFF Prescribed credits.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credit claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

time, cancer has become increasingly common, especially since the Industrial Revolution. This increase cannot be blamed on genetics; it has to do with the environment, including what we eat.

Empiric and epidemiologic research has shown that food can cause cancer.<sup>2,3</sup> Other research suggests that healthy foods prevent cancer and may even reverse the disease.<sup>4,5</sup> Still, clinicians lack data from large clinical trials of nutrition and cancer that could reveal more information. Until more researchers conduct such trials, it is important for clinicians to include nutrition education based on current evidence as part of discussions about cancer.

Certainly, it would be foolish to recommend that a patient reject cancer treatment and follow only a modified nutrition and lifestyle approach. There are instances of cancer reversals with a healthy diet and lifestyle changes; still, overall, those who choose only that route die more often than those who choose cancer treatment.<sup>6</sup> Cancer treatment is moving away from using only the toxic and damaging drugs of chemotherapy to include health-enhancing methods such as immunotherapy. Everyone should eat a healthy

diet, exercise daily, manage stress, engage in restorative sleep, and create social connections that can lead to meaning and purpose in life. Along with new health-enhancing cancer treatments, we could return to an earlier time when cancer was a rare disease. ■

## REFERENCES

1. Mukherjee S. *The Emperor of All Maladies: A Biography of Cancer*. New York: Simon and Schuster; 2010.
2. Doll R, Peto R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981;66:1191-1308.
3. Blot WJ, Tarone RE. Doll and Peto's quantitative estimates of cancer risks: Holding generally true for 35 years. *J Natl Cancer Inst* 2015;107(4). pii: djv044. doi: 10.1093/jnci/djv044.
4. Campbell TC, Jacobson H. *Whole: Rethinking the Science of Nutrition*. Dallas: BenBella Books; 2013.
5. Campbell TC, Campbell II TM. *The China Study: Revised and Expanded Edition: The Most Comprehensive Study of Nutrition Ever Conducted and the Startling Implications for Diet, Weight Loss, and Long-Term Health*. Dallas: BenBella Books; 2016.
6. The National Academies of Science, Engineering, and Medicine. A healthy diet alone will not cure cancer. Available at: <http://bit.ly/2L1xDae>. Accessed June 20, 2019.

## ABSTRACT & COMMENTARY

# Workplace Violence, Bullying Associated With Cardiovascular Disease Risk

**By Michael H. Crawford, MD**

*Professor of Medicine, Associate Chief for Education, Division of Cardiology University of California, San Francisco*

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

**SYNOPSIS:** In a 12-year follow-up of surveyed Scandinavian employees, reported workplace violence and bullying increased the risk of future cardiovascular disease of a magnitude similar to other recognized cardiovascular disease risk factors.

**SOURCES:** Xu T, Magnusson Hanson LL, Lange T, et al. Workplace bullying and workplace violence as risk factors for cardiovascular disease: A multi-cohort study. *Eur Heart J* 2019;40:1124-1134.

Herrmann-Lingen C. Victimization in the workplace: A new target for cardiovascular prevention? *Eur Heart J* 2019;40:1135-1137.

**W**orkplace stressors such as bullying and violence are associated with a higher risk of type 2 diabetes, but their role

in cardiovascular (CV) disease is unclear. From three large Scandinavian longitudinal studies of working men and women, Xu et al

studied four cohorts based on enrollment years ranging from 1995 to 2011. Employees aged 18-65 years with no prior CV disease and information available on workplace bullying and violence were identified. This resulted in a study population of more than 79,000 people. Workplace bullying and exposure to or threat of violence were obtained from self-administered questionnaires. CV disease was defined as first hospitalization for coronary or cerebral vascular disease. Other biographical data were obtained to assess confounders and other stressors at work that could influence the results. The subjects' mean age was 43 years; 53% of subjects were women.

The prevalence of bullying ranged from 8-13% over 12 months in the four cohorts. Mainly, the perpetrators were from within the company (79%), and 21% were clients. The prevalence of violence ranged from 7-17% over 12 months in the cohorts, and the perpetrators were mainly clients (91%). Only 10-14% of employees experienced both stressors at the same time. After a mean follow-up of 12.4 years, 3,229 CV events occurred in these employees. After adjustment for various covariates, bullying increased the risk of CV disease (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.28-1.40). Workplace violence also increased CV disease risk (HR, 1.25; 95% CI, 1.12-1.40). The frequency of bullying increased the risk (frequent HR, 2.22; 95% CI, 1.23-4.01). Frequent violence increased risk of cerebrovascular disease by 36%. The authors concluded that bullying and violence in the workplace are common and associated with a greater risk of developing CV disease.

#### ■ COMMENTARY

Previous studies have revealed that mental illnesses such as depression are independent risk factors for CV disease, as are certain personality traits, such as hostility and anger. Also, social risk factors, such as low socioeconomic status and stress, have been identified. Considering that workplace bullying and violence are related to some of the above risk factors, it is not

surprising that they would be independent risk factors, too. In this study, the population-attributable risk was 5% for bullying and 3% for violence, which is similar to other well-established risk factors such as diabetes (4%). In addition, a dose-response relationship was established for bullying, less so with violence. Sensitivity analyses with known confounders suggested these results were robust. Interestingly, there were no identified differences between the two sexes. Since such behavior potentially is modifiable, physicians and workplace managers need to be aware of these results.

There were limitations to this study. The authors relied on self-reporting on one day, and no further bullying or violence data were collected during follow-up. There is no information on underlying personality traits and behaviors, which could be important in understanding the results. It is possible that some victims may have exhibited negative behaviors that provoked inappropriate responses. Also, there may have been other stressors involved, such as marital conflict. The authors of these large studies did not provide data on clinical information such as blood pressure and cholesterol levels. Finally, this was a Scandinavian population, and the results may not be generalizable to other groups.

The main strengths of the study were the large population ( $> 79,000$  people) and the long follow-up (mean = 12 years). Also, it is biologically feasible that these work stresses could lead to anxiety, depression, overeating, increased alcohol consumption, impaired sleep, and hypertension, all of which would explain an increased incidence of CV disease. The weaker association with violence compared to bullying may be because almost all the violence was perpetrated by clients. The authors suggested that workers in these jobs may be self-selected for their ability to deal with irate clients better. In the final analysis, though, outcome studies that mitigate these behaviors need to be conducted to prove that eliminating bullying and violence would improve CV health. ■

## ABSTRACT & COMMENTARY

# The Return of Measles

By Stan Deresinski, MD

Clinical Professor of Medicine, Stanford University

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

**SYNOPSIS:** The number of measles cases in the United States has exceeded 1,000 so far in 2019, the largest number in 25 years.

**SOURCE:** Zimmerman LA, Muscat M, Singh S, et al. Progress toward measles elimination — European Region, 2009-2018. *MMWR Morb Mortal Wkly Rep* 2019;68:396-401.

On June 6, the CDC announced the number of measles cases for the year had exceeded 1,000, making this the largest outbreak in the United States in 25 years. An analysis of the 704 cases reported in the first

four months of 2019 found that 98% of outbreaks had occurred in U.S. residents and that 94% were associated with 13 individual outbreaks. Six of the 13 outbreaks occurred in underimmunized, "close-knit" communities.

The mean age of the cases was 5 years, but one-fifth were 20 to 49 years of age. Only 11% of cases were known to have been vaccinated. Of the total cases, 66 were hospitalized and 24 developed pneumonia. There were no fatalities.

## ■ COMMENTARY

The illness caused by measles virus infection is not trivial. Pneumonia can develop in those affected. Approximately one in 1,000 develop encephalitis, which often is fatal and results in devastating consequent long-term disability among survivors. The fatality rate is reported to be 1-2/1,000 and is higher in low-income countries. An additional, albeit quite rare, delayed complication that onsets seven to 10 years after infection is subacute sclerosing panencephalitis. Those at most risk of complications are individuals younger than 5 years of age and those older than 20 years of age, as well as pregnant women and those who are immunocompromised.

Measles is among the most readily transmissible of diseases, with a reproductive number as high as 12-18. This rate is twice as high as that of smallpox. Because transmission is airborne, only minimal exposure is necessary. The problem of high transmission is compounded by the fact that patients can transmit the virus for four days before the onset of the measles rash and for another four days after.

Perhaps among the strongest evidence of measles virus transmissibility is the fact that measles was an inevitable occurrence in children growing up in the United States before vaccine introduction. The CDC indicates that there had been a mean of 549,000 reported cases with 495 deaths reported each year in the United States in the decade prior to the introduction of the live measles vaccine in 1963. However, the CDC also indicates that measles had been vastly underreported and that the actual number of yearly cases had been closer to 3 to 4 million.

On a global scale, 19 cases per 1 million persons are reported each year, with an estimated 89,780 deaths. This is a vast underestimate of the true problem because of underreporting and because it is estimated that, in fact, 2 to 3 million people die of measles annually. The global problem of measles is not limited to low-income countries. There has been a resurgence of measles in several European countries, largely because of resistance to vaccination. In 2018, the WHO European Region reported the highest number of confirmed cases in 20 years, with 80,000 cases identified in 53 countries. Five hundred or more cases were reported from each of 14 countries, including four countries where the infection had been declared eliminated — Israel, Greece, Albania, and the United Kingdom. Americans visit three of these countries frequently and, thus, serve as a potential source of infection that can be transported to the United States. Among

the countries from which importations have occurred recently are England, Germany, India, the Philippines, Ukraine, and France.

Measles vaccine is among the most effective vaccines available and, in theory, could eradicate the infection worldwide. The number of global deaths prevented by its use since 2000 is estimated to be 21 million. However, there was a 31% increase in the reported number of global cases between 2016 and 2017, a measure of the failure of public health systems and of the emerging vaccine hesitancy.

Community vaccination rates of 95% are associated with strong herd immunity and protection. Although the use of a single dose of the attenuated live vaccine had been significantly effective, the occurrence of outbreaks in school-age children in 1989 led to a recommendation to administer a second dose to all children. A second dose increases vaccine efficacy from approximately 93% to 97%. Its introduction led to a further decrease in the annual number of cases. In 2000, measles was officially declared eradicated in the United States, a designation that requires the absence of endemic transmission for three years. Since 2000, the number of cases has been as low as 37 in 2004 and as high as 667 in 2014 — an incidence that was surpassed in 2019 by April 26.<sup>1</sup>

It is critical for everyone to be up to date regarding measles immunity. Among those to whom special attention should be paid are international travelers. Acceptable presumptive evidence of adequate vaccination consists of written documentation, laboratory evidence of immunity, laboratory confirmation of measles, or birth before 1957.<sup>2</sup> The 2019 U.S. outbreak is largely the result of two factors: the introduction of infection by unvaccinated travelers returning from abroad where they acquired the infection, and subsequent exposure of other unvaccinated individuals, many of whom reside in communities that, for religious or other reasons (especially access to misinformation), resist vaccination.

Vaccine hesitancy requires collaboration among health-care providers, parents, government, public health, technology companies, and civil society at large to deal with the misinformation about vaccination in general.<sup>3</sup> Failure will mean more measles and, potentially, loss of inclusion in the list of countries that have eliminated this dangerous infection. ■

## REFERENCES

1. Centers for Disease Control and Prevention. Measles cases in 2019. Available at: <http://bit.ly/2XjPvI3>. Accessed June 25, 2019.
2. Centers for Disease Control and Prevention. Routine measles, mumps, and rubella vaccination. Available at: <http://bit.ly/31SlzYy>. Accessed June 25, 2019.
3. The Lancet Child Adolescent Health. Vaccine hesitancy: A generation at risk. *Lancet Child Adolesc Health* 2019;3:281.

---

## ABSTRACT & COMMENTARY

# Statin Use Moderately Reduces Dementia Risk After Concussions in Older Individuals

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College

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

**SYNOPSIS:** In a large population study, concussion in older adults resulted in significantly higher risk for dementia that was modestly lower among those taking a statin.

**SOURCE:** Redelmeier DA, Manzoor F, Thiruchelvam D. Association between statin use and risk of dementia after a concussion. *JAMA Neurol* 2019; May 20. doi: 10.1001/jamaneurol.2019.1148. [Epub ahead of print].

**D**ue to the strong association of traumatic brain injury with chronic traumatic encephalopathy, concussions are a growing concern, especially for young adults playing contact sports. However, the long-term risk for dementia in older adults diagnosed with a concussion and whether any medications can affect this risk are unclear. Therefore, Redelmeier et al conducted a large population-based, double cohort study using linked databases to examine if statin and other medication use was associated with a higher or lower risk of dementia in older adults after a concussion.

Over a 20-year period (April 1, 1993, to April 1, 2013), patients 66 years of age and older who were diagnosed with a concussion were identified based on physician billing data using the ICD-9 code from the Ontario Health Insurance Plan. To reduce confounding from severe brain injury, patients who were admitted to a hospital within two days of a concussion or who survived less than 90 days were excluded. To reduce confounding from past neuropsychiatric conditions, patients with a history of dementia or delirium in the prior five years were excluded. The Ontario Drug Benefit Program database provided data on the prescription status of statin and other medications. The primary study outcome was a physician diagnosis of dementia based on ICD-9 codes.

Redelmeier et al identified 28,815 patients (median age, 76 years; 61.3% female) with a diagnosis of concussion, with 7,058 patients receiving a statin during the 90 days after a concussion. The demographic characteristics were similar between patients receiving statins and those who did not. A total of 4,727 patients in the study developed dementia over a mean follow-up of 3.9 years after a concussion. Statin use was associated with a modest 13% (95% confidence interval [CI], 7%-19%;  $P < 0.001$ ) reduced risk of dementia compared with patients who did not receive a statin (relative risk, 0.87; 95% CI, 0.81-0.93;  $P < 0.001$ ). After adjusting for all baseline characteristics, statin use was associated with a 16% (95% CI,

10%-22%;  $P < 0.001$ ) reduction in risk of subsequent dementia.

Reduced dementia risk was specific to statins, as no other lipid-lowering or cardiovascular medications were associated with a consistent decrease in dementia risk, with the possible exception of angiotensin II receptor blockers. Additionally, benzodiazepines, thyroid supplements, gastric acid suppressors, inhaled bronchodilators, and glaucoma eye drops were not associated with a lower risk of subsequent dementia. Secondary analyses revealed the largest risk reduction with rosuvastatin and smallest with simvastatin.

Similarly, hydrophilic statins (i.e., rosuvastatin and pravastatin) were more beneficial than lipophilic statins (i.e., all other statins). A higher dose of statins produced similar benefits as a lower dose of statins. Furthermore, in a parallel analysis of dementia risk after an ankle sprain, the authors found that statin use was associated with only a 5% (95% CI, 3%-8%;  $P < 0.001$ ) reduction in the risk of dementia. Finally, statin use was associated with an insignificant increased risk of depression after a concussion.

## ■ COMMENTARY

A major strength of this study was the relatively large sample size with long follow-up. This could be a result of the investigators leveraging a large population in Ontario with universal healthcare that was linked to multiple databases. Additionally, because of these databases, the investigators conducted detailed statistical analyses on the nuances of statin use (e.g., specific statin, type of statin, dosage of statin, etc.) that often are unavailable in similar studies. Another significant strength was the use of a second cohort to investigate the association of statin use and the development of dementia in patients after an ankle sprain, which helped to effectively differentiate the stronger beneficial effect of statin use specifically after brain injury.

This study was well designed, but there were significant limitations. First, this was not a randomized trial. There may be significant confounders due to earlier indications for statin use. Additionally, several important covariates, including smoking history, daily exercise, and other factors that may affect dementia risk, were missing from the dataset. Although ICD-9 codes for concussion are more reliable than using self-reported measures, diagnosis codes for concussion and dementia are not fully

sensitive and may underestimate the true incidence. This study also would miss any patients who had sustained a concussion but never received medical attention.

Finally, the study authors relied on the use of aggregate data and broad diagnostic codes of concussion and dementia, which are highly varied disorders. It is unclear if these results could be translated to clinical care at an individual patient level. ■

## PHARMACOLOGY UPDATE

# Galcanezumab-gnlm Injection (Emgality)

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 the first drug to reduce the frequency of episodic cluster headache. Galcanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand, blocking its binding to the CGRP receptor. Researchers believe CGRP plays an active role in migraine and cluster headaches. Galcanezumab was approved in September 2018 for the prevention of migraine headaches. It is distributed as Emgality.

### INDICATION

Galcanezumab is indicated for the preventive treatment of migraine and treatment of episodic cluster headache.<sup>1</sup>

### DOSAGE

The recommended dose for episodic cluster headache is 300 mg (three consecutive subcutaneous injections of 100 mg) at the onset of the cluster period and then monthly until the end of the cluster period.<sup>1</sup> Sites of administration include the abdomen, thigh, back of upper arm, or buttocks. Galcanezumab is available as a 100 mg/mL single-dose, prefilled syringes as well as 120 mg/mL prefilled pens and syringes.

### POTENTIAL ADVANTAGES

In addition to providing a new mechanism of action, galcanezumab also is the first FDA-approved drug to reduce the frequency of episodic cluster headaches.

### POTENTIAL DISADVANTAGES

The most common adverse reaction is injection site reactions (e.g., pain, erythema, and pruritus).<sup>1</sup> The incidence of anti-galcanezumab antibodies ranges from 4.8% to 12.5% after six to 12 months of treatment, respectively.<sup>1</sup> These are mostly neutralizing antibodies. The clinical significance is unclear at this time.<sup>1</sup>

### COMMENTS

The efficacy of galcanezumab was evaluated in a randomized, eight-week, double-blind, placebo-controlled study. Subjects included those with episodic cluster headache who experienced a maximum of eight attacks per day, a minimum of one attack every other day, and at least four attacks during the prospective seven-day baseline period.<sup>1</sup> Subjects were excluded if they showed ECG abnormalities or presented with a history of myocardial infarction, unstable angina, cardiac procedures (percutaneous transluminal coronary angioplasty, bypass grafting), deep vein thrombosis, pulmonary embolism, stroke, intracranial or carotid aneurysm, peripheral vascular disease, or Raynaud's disease. Subjects were randomized to either galcanezumab (n = 49) or placebo (n = 57). Certain rescue medications, such as triptans, oxygen, acetaminophen, or nonsteroidal anti-inflammatory drugs, were permitted. The primary efficacy endpoint was the mean change from baseline in weekly cluster headache attack frequency across week 1 to week 3. The secondary endpoint was the percentage of subjects achieving a 50% reduction (responders) in frequency of weekly cluster attack at week 3. Galcanezumab showed a mean 49% reduction from a baseline frequency of 17.8% compared to a 30% reduction from a baseline of 17.3% for placebo ( $P = 0.036$ ). Responder rates were 71.4% vs. 52.6% ( $P = 0.046$ ).

### CLINICAL IMPLICATIONS

Cluster headache is a rare, extremely debilitating, trigeminal autonomic cephalgia.<sup>2,3</sup> The estimated lifetime prevalence is about 0.12%, with higher prevalence in males. Episodic cluster headaches are more prevalent than the chronic type.<sup>3</sup> Generally, cluster headache is more severe than migraine, but with shorter duration and accompanied by autonomic symptoms (e.g., watery eyes

PHYSICIAN EDITOR  
Stephen A. Brunton, MD  
Adjunct Professor of Pharmacy Practice  
College of Pharmacy  
Roseman University of Health Sciences  
Salt Lake City

PEER REVIEWER  
Gerald Roberts, MD  
Senior Attending Physician  
Long Island Jewish Medical Center  
N/S/LIJ Health Care System, New Hyde Park, NY

EDITORIAL ADVISORY BOARD  
James Chan, PharmD, PhD  
Associate Clinical Professor  
School of Pharmacy  
University of California, San Francisco

William T. Elliott, MD, FACP  
Assistant Clinical Professor of Medicine  
University of California, San Francisco

David Fiore, MD  
Professor of Family Medicine  
University of Nevada, Reno

Ken Grauer, MD  
Professor Emeritus in Family  
Medicine, College of Medicine,  
University of Florida

Seema Gupta, MD, MSPH  
Clinical Assistant Professor;  
Department of Family and Community  
Health, Joan C. Edwards School of Medicine  
Marshall University  
Huntington, WV

Harold L. Karpman, MD, FACC, FACP  
Clinical Professor of Medicine  
David Geffen School of Medicine at UCLA

Louis Kuritzky, MD  
Clinical Assistant Professor;  
University of Florida, Gainesville

Martin S. Lipsky, MD  
Chancellor, South Jordan Campus, Roseman  
University of Health Sciences, South Jordan, UT

Joseph E. Scherer, MD, MPH  
Core Faculty,  
Eisenhower Health Family Medicine Residency  
Program,  
Eisenhower Health Center, La Quinta, CA;  
Clinical Professor;  
Keck School of Medicine,  
University of Southern California, Los Angeles

Allan J. Wilke, MD, MA  
Professor and Chair  
Department of Family Medicine  
Western Michigan University  
School of Medicine, Kalamazoo

EDITOR  
Jonathan Springston

EDITORIAL GROUP MANAGER  
Leslie Coplin

ACCREDITATIONS MANAGER  
Amy M. Johnson

and runny nose). Cluster headaches may occur several times a day lasting between 15 minutes and three hours.<sup>2</sup> Those with episodic headaches may experience freedom from headache for periods of months or years. Those with chronic headaches experience no remission or only enjoy a period free from headaches lasting less than one month.<sup>4</sup>

Currently, cluster headaches are not treated optimally. The American Headache Society Evidence-Based Guidelines and The American Academy of Neurology quality criteria recommend subcutaneous sumatriptan, intranasal zolmitriptan, and high-flow oxygen for acute treatment.<sup>5,6</sup> Sumatriptan injection, approved for acute treatment, provides headache relief in 75% of patients compared to 26–35% for placebo.<sup>7</sup> There are no approved effective treatments for reducing the frequency of attacks prior to galcanezumab, although suboccipital corticosteroid injection has established effectiveness off-label.<sup>5</sup> Galcanezumab, as well as fremanezumab (the other FDA-approved CGRP ligand monoclonal antibody), have not shown efficacy in preventing chronic cluster headaches.<sup>8</sup> The maker of fremanezumab recently terminated its study for the prevention of episodic cluster headache due to early indications of insufficient effectiveness.<sup>9</sup> The cost of galcanezumab for 300 mg (3 × 100 mg) is \$1,725. ■

## REFERENCES

- Eli Lilly and Company. Emgality Prescribing Information. Available at: <http://bit.ly/2NbQ6Ny>. Accessed June 24, 2019.
- U.S Food & Drug Administration. FDA approves first treatment for episodic cluster headache that reduces the frequency of attacks, June 4, 2019. Available at: <http://bit.ly/2ZOTpf>. Accessed June 24, 2019.
- Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: A meta-analysis of population-based studies. *Cephalgia* 2008;28:614-618.
- American Migraine Foundation. Understanding Cluster Headache, April 18, 2019. Available at: <http://bit.ly/2X8wj6w>. Accessed June 24, 2019.
- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of cluster headache: The American Headache Society Evidence-Based Guidelines. *Headache* 2016;56:1093-1106.
- Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology* 2010;75:463-473.
- GlaxoSmithKline LLC. Imitrex Prescribing Information, July 2018. Available at: <http://bit.ly/2XqeY8p>. Accessed June 24, 2019.
- Tepper SJ. Anti-calcitonin gene-related peptide (CGRP) therapies: Update on a previous review after the American Headache Society 60th Scientific Meeting, San Francisco, June 2018. *Headache* 2018;58 Suppl 3:276-290.
- Smith A. Teva abandons Ajovy trial for cluster headaches. *PharmaTimes*, April 24, 2019. Available at: <http://bit.ly/2I4cP95>. Accessed June 24, 2019.

## CME QUESTIONS

- Which of the following is associated with a higher cancer risk?
  - Dairy products
  - Processed red meat
  - Processed white meat
  - Candy bars
- In a report from Scandinavia, workplace violence almost always is perpetrated by:
  - coworkers.
  - clients.
  - management.
  - security.
- Which of the following statements is true regarding measles?
  - In an analysis of the first 704 reported cases of measles in the United States in 2019, only 28% occurred in U.S. residents.
  - Ninety-five percent of reported measles cases in 2019 in the United States occurred in children younger than 5 years of age.
  - Measles is predominantly transmitted by direct contact.
  - Measles is transmissible from a patient for approximately four days prior to development of a rash.

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand. Call us at (800) 688-2421 or email us at [reprints@reliasmedia.com](mailto:reprints@reliasmedia.com).

Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at [groups@reliasmedia.com](mailto:groups@reliasmedia.com) or (866) 213-0844.

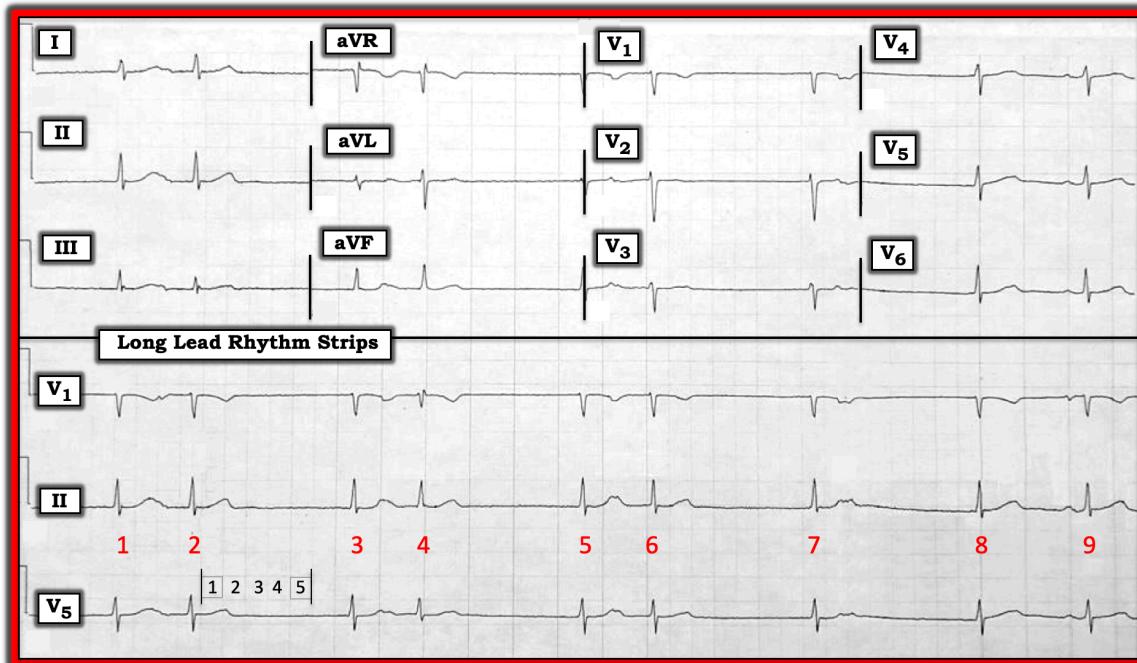
To reproduce any part of Relias Media newsletters for educational purposes, please contact The Copyright Clearance Center for permission at [info@copyright.com](mailto:info@copyright.com) or (978) 750-8400.

*Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

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

## What Observations Can One Make?

The rhythm in the figure below is challenging to interpret. More than one answer is possible. Unfortunately, no clinical information was available on the patient. What observations can one make about the cardiac rhythm?



This tracing was recorded at the standard 25 mm/second speed. Because the ECG grid is faded, I have indicated the size of a large box with a small gray square. Also, I show the duration of five large boxes in black numbers at the bottom of the tracing. I am not after a precise interpretation of this rhythm. Atrial activity is difficult to make out because of its small size. Unless one has calipers readily available, it is unlikely one can evaluate some details. What counts is appreciating the principal findings. So what are they? The rhythm in the figure is supraventricular because all QRS complexes are narrow. The overall heart rate is slow. There are several other important observations to make.

There is group beating for at least the first part of the tracing. That is, a short-long (or bigeminal) pattern is seen for the first six beats. Recognition of group beating is helpful because it suggests that some form of Wenckebach conduction may be present. Beat 9 appears to be sinus-conducted. In the long lead II rhythm strip, an upright P wave with normal PR interval precedes this QRS complex. Looking at the three long lead rhythm strips (taken from leads V1, II, and V5), no P wave precedes beats 1, 3, 5, 7, or 8. The R-R interval preceding each of these beats appears to be equal and approximately seven large boxes in duration. This corresponds to a heart rate just

over 40 beats/minute. These are junctional escape beats. There appear to be other indications of periodic atrial activity. This is seen best in lead V1. Note the small, notched deflection in lead V1 that appears midway within the R-R interval between beats 1 and 2. In the long lead V1, does it look like there also is some subtle notching toward the end of the ST segment of beats 3, 5, and 7?

There is a phenomenon known as “escape-capture” bigeminy in which junctional escape beats are followed by atrial activity that “captures” (i.e., conducts to) the ventricles. This appears to be happening for the first six beats in the tracing. The subtle notching (P wave) that occurs within the ST segment of beat 7 is not conducted to the ventricles. There follows another junctional beat (beat 8). Finally, a sinus P wave conducts normally to the ventricles (beat 9). The fundamental rhythm disturbance in this tracing is marked bradycardia. Thus, a junctional escape rhythm arises with escape-capture until a P wave is nonconducted. This allows the sinus P wave that precedes beat 9 to regain control of the rhythm.

For a more detailed analysis of this cardiac rhythm, together with laddergram illustration of the probable mechanism, please visit: <http://bit.ly/2L4TwPM>.