12-14-19

Flu Season Kicks Off Early with Influenza B Making Unexpected Appearance

By Kelly Young *Edited by Susan Sadoughi, MD, and André Sofair, MD, MPH*

The influenza season got its earliest start in the U.S. in 15 years, with the South being hit particularly hard, the Associated Press reports.

The B strain of the influenza virus has made an early appearance this flu season, according to the CDC. Influenza B/Victoria viruses are more common than the A strains so far this year. Normally, the B strains show up later in the season, around March or April.

The B strains are the most common strains causing illness among those aged 0–4 years (46% of reported viruses) and those aged 5–24 (60%). Among the other findings:

- So far, officials estimate that 1.7 million people have been sickened by influenza this season. This includes 16,000 hospitalizations and 900 flu-related deaths.
- So far this season, six children have died from influenza.
- Sixteen states are reporting widespread flu activity, and 12 states have intense activity, including much of the South.

CDC flu surveillance

AP story

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Obstet Gynecol 2019 Dec; 134:1219

Good News About Nonopioid Options for Postpartum Pain Control

Ibuprofen did not raise postpartum blood pressure.

Nonsteroidal anti-inflammatory agents are effective in reducing pain but may raise blood pressure (BP) in adults with chronic hypertension. To evaluate whether ibuprofen affects BP in women with hypertensive disorders of pregnancy and mild hypertension during the immediate postpartum period, researchers conducted a double-blind randomized trial involving 61 such women; of these, 31 received ibuprofen (600 mg every 6 hours) and 30 received acetaminophen (650 mg every 6 hours). BP was assessed every 4 hours, yielding an average of 17 measurements per participant prior to hospital discharge.

Postpartum average arterial pressure did not differ between groups. There was no difference in the proportion of participants who requested additional breakthrough medications after either vaginal or cesarean delivery. In both study groups, overall pain control was good, with average pain scores substantially below the self-reported "acceptable level." Breakthrough opioid medications were requested by 24% of women in the ibuprofen group and 30% in the acetaminophen group (P=0.62).

COMMENT: This study provides reassurance that both acetaminophen and ibuprofen can be safely used as narcotic-sparing analgesics in the postpartum setting, even for women with hypertensive disorders of pregnancy and mild hypertension in the immediate postpartum period. A future study should examine whether the combination of acetaminophen and ibuprofen provides postpartum women with additional benefit.

CITATION(S): Penfield CA et al. Ibuprofen and postpartum blood pressure in women with hypertensive disorders of pregnancy: A randomized controlled trial. *Obstet Gynecol* 2019 Dec; 134:1219. (https://doi.org/10.1097/AOG.0000000000003553)

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Lancet Neurol 2019 Nov 6

Blood Pressure Treatment, Incident Dementia, and Alzheimer Disease: A Meta-Analysis

Promising evidence that antihypertensive treatment decreases incident dementia and AD risk

Hypertension is a risk factor for dementia. In this meta-analysis, researchers analyzed data from six prospective community-based studies to determine if antihypertensive drug treatment was associated with dementia or Alzheimer disease (AD) risk in participants who were dementia-free and aged ≥55 at baseline. Major antihypertensive treatment classes included angiotensin II receptor blockers, angiotensin-converting–enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics. Participants were classified as normotensive (blood pressure <140/90 mm Hg) or hypertensive (≥140/90 mm Hg). Normotensive individuals included those with treated hypertension. Incident dementia or AD was determined by accepted criteria.

Among 31,090 individuals (50%–60% women; mean age, 59–77; median follow-up, 7–22 years), 3728 developed dementia and 1741 developed AD. After accounting for confounding variables (including smoking, education, and baseline blood pressure), in the hypertensive group, antihypertensive use significantly decreased the risks for dementia (by 12%) and AD (by 16%), compared with those not on antihypertensive medications. In apolipoprotein E Ɛ4 carriers with hypertension, antihypertensive use was associated with a significant 23% decreased risk for dementia. No significant differences in dementia or AD risk were seen among antihypertensive medication classes. In the normotensive group, dementia and AD risk did not differ with versus without antihypertensive use.

COMMENT: Treating hypertension with appropriate use of any antihypertensive medication class may decrease dementia risk, even in those with mild cognitive impairment (MCI). The baseline cohorts in this meta-analysis were predominantly white and included individuals with MCI. Whether these promising results also translate to other races requires further study.

CITATION(S): Ding J et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: A meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol* 2019 Nov 6; [e-pub]. (https://doi.org/10.1016/S1474-4422(19)30393-X)

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Obstet Gynecol 2019 Dec; 134:1245

Aiming for Vaginal Birth After a Previous Failed Vacuum-Assisted Attempt That Led to Cesarean Delivery

In a study in Israel, two thirds of women with a history of failed vacuum-assisted delivery had success with a subsequent trial of labor after cesarean.

To reduce maternal morbidity and healthcare costs associated with cesarean delivery, many providers continue to encourage vaginal birth after cesarean (VBAC) in appropriate candidates. Vacuum-assisted vaginal deliveries (VAVD) account for 3% of all deliveries, and failure rates of attempted VAVD range from 5% to 10%. Although the overall success rate of trial of labor after cesarean (TOLAC) is as high as 80%, few studies have addressed this success rate specifically in patients who required cesarean delivery after a failed VAVD.

In a retrospective cohort study in Israel, among 113 patients with previous failed VAVD who attempted a TOLAC in their next pregnancy, 76 (67%) went on to have a successful VBAC. Among the 37 failed TOLAC attempts, 23 women reached full cervical dilation but failed to delivery vaginally, 2 never reached full cervical dilation, and 12 required repeat cesareans due to nonreassuring fetal status. Apgar scores associated with failed TOLACs were lower than those after successful TOLACs; however, Apgar scores after elective repeat cesareans were similar to those after successful TOLACs. In addition, women with successful TOLACs had no anal sphincter injuries, postpartum hemorrhage, or uterine rupture.

COMMENT; Counseling women about TOLAC can be challenging as it requires an enormous amount of information exchange. Nonetheless, these results demonstrate that a failed VAVD should not prevent a woman from attempting a VBAC. Although the study's retrospective design does not allow definitive recommendations for women with prior failed VAVD, VBAC rates were similar to those of all women pursuing TOLAC; accordingly, reassuring such patients regarding safety and their likelihood of success appears reasonable.

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CITATION(S): Levin G et al. Subsequent pregnancy outcomes after failed vacuum-assisted delivery. *Obstet Gynecol* 2019 Dec; 134:1245. (https://doi.org/10.1097/AOG.0000000000003527)

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N Engl J Med 2019 Nov 28; 381:2091

Do Women with Extremely Dense Breasts Benefit from Supplemental MRI Screening?

Breast MRI detected more cancers but also led to more biopsies that were benign.

Women with extremely dense breast tissue have excess risk for developing breast cancer; however, no specific guidelines address the evaluation of such women. In a Dutch trial, 40,000 women (age range, 50–75) with extremely dense breasts and a recent negative screening mammogram were randomized to undergo — or not undergo — supplemental breast MRI.

Among women assigned to breast MRI, 59% actually underwent MRI imaging; among those women, 95 per 1000 were recalled for further evaluation, and breast cancer was detected in 16 per 1000. MRI-detected cancers were more likely to be small and categorized as ductal carcinoma in situ. The rate of interval cancers within 2 years (the interval before the next routine biennial mammogram) was significantly lower in the breast MRI group than in the mammography-alone group (2.5 vs. 5.0 per 1000 screens). The positive predictive value of MRI was 17%, and 74% of biopsies ordered based on MRI findings were benign.

COMMENT: These results confirm that breast MRI is more sensitive than mammography for detecting breast cancer in women with extremely dense breasts; however, this approach has low specificity and can lead to benign biopsies. Furthermore, it's not clear whether supplemental imaging can reduce breast cancer mortality; without long-term follow-up, incidence of interval cancer serves as a surrogate for mortality. Cost-effectiveness, risk for over-diagnosis and treatment of nonlethal indolent cancers, potential harms of unnecessary biopsies, and patients' anxiety all must be considered. Lastly, not all women with dense breasts as their only risk factor will necessarily benefit from an MRI; individualized risk assessment might be better for identifying high-risk women (lifetime risk >20%) who would benefit from MRI screening.

CITATION(S): Bakker MF et al. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med* 2019 Nov 28; 381:2091. (https://doi.org/10.1056/NEJMoa1903986)
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JAMA Oncol 2019 Sep 19; 5:1589

Breast Cancer May Be Biologically Different in Men Than in Women

Even after controlling for multiple factors, 3-year mortality was 15% higher in men.

The approach to treating breast cancer in men is largely the same as in women. However, large studies of treatments for men have been hard to come by, as the number of male breast cancer patients is small, even in large referral centers.

To compare outcomes between men and women with breast cancer, investigators conducted a retrospective cohort study involving 16,000 men (median age, 63.3 years) and 1.8 million women (median age, 59.9 years) in the National Cancer Database who were diagnosed with breast cancer from 2004 through 2014. Race, ethnicity, clinical characteristics, treatment, and accessibility to care were taken into account.

At median follow-up of 54.0 months for men and 60.5 months for women, overall survival (the primary outcome) was significantly worse for men than for women (45.8% vs. 60.4%); also worse were 3-year survival (86.4% vs. 91.7%) and 5-year survival (77.6% vs. 86.4%). Even after controlling for multiple factors, 3-year mortality was 15% higher in men than in women. A striking finding was that survival was inferior in men particularly early after diagnosis. As in other reports, males were typically older than women at presentation and were more likely to have higher-stage disease and be undertreated, regardless of stage. They were also more likely to have Recurrence Scores that were very high (≥31) or very low (≤11).

COMMENT: These findings suggest that breast cancer in men may be different biologically than breast cancer in women. By extension, outcomes may be different as well. That said, this analysis also highlights, as other reports have suggested, that male patients present with more advanced disease, perhaps because of lack of awareness, and they often receive less than optimal treatment and are less compliant with treatment than their female counterparts.

CITATION(S): Wang F et al. Overall mortality after diagnosis of breast cancer in men vs women. *JAMA Oncol* 2019 Sep 19; 5:1589. (https://doi.org/10.1001/jamaoncol.2019.2803)
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Nature 2019 Oct; 574:264

One Fungal Genus Is Linked Strongly to Pancreatic Cancer

Malassezia-*triggered tumor growth involves activation of the C3 complement cascade.*

A meticulous series of experiments links one particular fungal genus to pancreatic cancer. Researchers showed that fungi from the genus *Malassezia* (particularly, *M. globosa*) travel from the gut through the sphincter of Oddi to the pancreas. Both in human pancreatic cancer and in a genetically engineered mouse model that develops pancreatic cancer, this fungal species is present in concentrations 3000 times higher than its concentrations in normal or benignly inflamed pancreatic tissue — an association not seen with any other gut fungi. Is this fungus an opportunistic colonizer of tumor tissue, or does the fungus encourage growth of the tumor?

In the mouse model, eliminating the fungus from the gut early in life slowed development of pancreatic cancer, and repopulating the mice with *Malassezia* (but not with other fungi) triggered tumor growth. The mechanism by which the fungus triggered tumor growth involved inflammation, particularly activation of the C3 complement cascade. The investigators think pancreatic tumors somehow encourage growth of *Malassezia* in the gut and the fungus then homes to the tumor and enhances tumor growth.

COMMENT: This intriguing study incriminates the fungal genus *Malassezia*, and particularly *M. globosa*, as a factor in pancreatic cancer. Interestingly, *M. globosa* is a cause of dandruff and previously has not been considered to be a gut pathogen. By linking pancreatic cancer to a particular organism, and by identifying the molecular mechanism by which the organism stimulates tumor growth, this research suggests new targets for attacking this malignancy.

CITATION(S): Aykut B et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature* 2019 Oct; 574:264. (https://doi.org/10.1038/s41586-019-1608-2)

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Science 2019 Oct 25; 366:447

Racial Bias in Algorithms Used to Identify Patients Who Need Special Attention

One large health system's algorithm was less likely to recommend interventions for black patients at any level of illness severity.

Many U.S. health systems use proprietary algorithms that analyze electronic medical record data to identify patients who are particularly at risk for adverse health outcomes in hopes of intervening to prevent those outcomes. To examine potential racial disparities in algorithms' recommendations, investigators obtained a medical record dataset from a large health system that covered more than 100,000 patient-years. The dataset included elements used to predict outcomes and the outcomes themselves. Investigators also were given the algorithms' inputs (e.g., demographics not including race, insurance type, diagnosis and procedure codes, medications, and detailed costs) and outputs.

The algorithm assumed that patients who were projected to have the greatest future cost had the greatest need for intervention. However, when self-reported race was taken into account, black patients were sicker than white patients by measures other than cost (e.g., greater number of chronic illnesses) and generated fewer costs at any level of illness severity — because they received less care. Thus, at any level of illness severity, the algorithm was more likely to recommend preventive interventions for white patients than for black patients. The algorithm-maker confirmed these findings on a much larger dataset.

COMMENT: Electronic record databases could be powerful tools to identify patients who need preventive interventions. But these findings argue that, if analytic techniques are suboptimal, programs designed to protect patients might, instead, be harmful to some.

CITATION(S): Obermeyer Z et al. Dissecting racial bias in an algorithm used to manage the health of populations. *Science* 2019 Oct 25; 366:447. (https://doi.org/10.1126/science.aax2342)
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Ann Intern Med 2019 Nov 5; 171:643

Colorectal Cancer Screening in Asymptomatic Average-Risk Adults

The American College of Physicians reconciles various published guidelines in its guidance statement for colorectal cancer screening.

Sponsoring Organization: American College of Physicians (ACP)

Background: Because guidelines for colorectal cancer (CRC) screening vary in recommended tests and ages to start and stop screening, the ACP graded recommendations from six recent major guidelines (American College of Radiology, American Cancer Society [ACS], U.S. Preventive Services Task Force, Canadian Task Force on Preventive Health Care, U.S. Multi-Society Task Force on Colorectal Cancer [MSTF], and Scottish Intercollegiate Guidelines Network) to offer summary guidance.

Key Recommendations

- Average-risk adults with life expectancy of >10 years should start screening at age 50 and should discontinue screening after age 75. When comorbid conditions shorten life expectancy, patients might not reap benefits of screening.
- CRC screening test selection should be based on patient–clinician shared decision making, with discussion of specific tests' benefits, harms, costs, availability, and frequency. Recommended screening test options include (1) fecal immunochemical testing (FIT) or high-sensitivity guaiac-based fecal occult blood testing every 2 years; (2) colonoscopy every 10 years; or (3) flexible sigmoidoscopy every 10 years plus FIT every 2 years. Positive results on any noncolonoscopy screening test require referral for colonoscopy.
- The ACP discussed multitarget stool DNA testing (Cologuard) and computed tomography colonography but did not recommend them, because supporting evidence is currently limited.

COMMENT — GENERAL MEDICINE
Daniel D. Dressler, MD, MSc, SFHM, FACP

The ACP does not endorse an earlier screening start age of 45, which is recommended by the ACS (for all patients) and the MSTF (for black patients) because of the much lower frequency of CRC in younger patients. The average time to prevent 1 death from CRC per 1000 people screened (across the 50–75 age span) is 10.3 years. This guidance statement does not address symptomatic patients or patients at high risk for CRC (e.g., based on positive family history).

COMMENT — GASTROENTEROLOGY
Charles J. Kahi, MD, MS

This ACP guidance statement is based on an exhaustive and rigorous review of the evidence. In addition to maintaining 50 years as the starting age for CRC screening in average-risk individuals, a notable recommendation is for biennial fecal

testing. This is a departure from current practice in the U.S. where annual testing is generally used and is favored by cost-effectiveness analyses.

CITATION(S): Qaseem A et al. Screening for colorectal cancer in asymptomatic average-risk adults: A guidance statement from the American College of Physicians. *Ann Intern Med* 2019 Nov 5; 171:643. (https://doi.org/10.7326/M19-0642)
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JAMA Netw Open 2019 Nov 1; 2:e1914078

Do U.S. Policies That Punish Pregnant Women for Drug Use Actually Work?

States with punitive policies had higher rates of neonatal abstinence syndrome, suggesting deleterious effects of such laws.

To tackle drug use during pregnancy, several states have enacted punitive laws (defined as criminalization, grounds for civil commitment, or child abuse or neglect) or reporting laws (defined as duty to report to authorities). To examine the potential adverse effects of such mandates, investigators examined rates of neonatal abstinence syndrome (a proxy for maternal opioid use) in 8 states among >4.5 million births from 2003 through 2008.

Adjusted rates of neonatal abstinence syndrome were 46 per 10,000 live births in states without punitive policies, 57 per 10,000 in states during the first year after enactment of punitive policies (odds ratio, 1.25), and 60 per 10,000 more than 1 year after enactment (OR, 1.33). States with reporting laws did not have significantly higher rates of neonatal abstinence syndrome.

COMMENT: The implementation of punitive policies toward pregnant drug users was associated with higher rates of neonatal abstinence syndrome, a serious adverse outcome of drug use with an estimated annual hospital cost of >$500 million for neonatal care. Such policies deter women from seeking prenatal care and limit opportunities for referrals for treatment of substance use. This echoes the observation of poorer pregnancy outcomes in states with limited access to the full range of reproductive services.

CITATION(S): Faherty LJ et al. Association of punitive and reporting state policies related to substance use in pregnancy with rates of neonatal abstinence syndrome. *JAMA Netw Open* 2019 Nov 1; 2:e1914078. (https://doi.org/10.1001/jamanetworkopen.2019.14078)
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Pediatrics 2019 Dec 2; e20191071

Universal Background Checks Reduce Gun Carrying by Youth

States that require universal background checks at the point of firearm sales had significantly lower rates of youth who carry firearms.

Even though adolescents are prohibited from purchasing guns, guns can be obtained through “straw purchase” or from family or friends. Firearms are involved in roughly 86% of homicides and 43% of suicides among youth and young adults. In 1998, the National Instant Criminal Background Check System (NICS) was implemented. Using data from the National Youth Risk Behaviors Survey (a nationally representative sample of students in grades 9 to 12) from 1993 to 2017,

researchers determined whether the NICS in combination with state laws requiring universal background checks reduced gun carrying by adolescents.

On average, 6% of students in grades 9 to 12 carried guns during the study period. Older adolescents (16 to 18 years), males, and whites were more likely to carry guns. Of those who carried guns, significantly fewer were from states with universal background check laws than from states without such laws (17% vs. 83%). Before implementation of the NICS, rates of gun carrying by adolescents did not differ between states with and without universal background check laws. After implementation, these rates were lower in states with such laws.

COMMENT: State laws that require universal background checks on all prospective gun buyers are very effective in reducing gun carrying by youth. If we consider gun violence in youth a public health crisis, advocating in our states for laws that require universal background checks prior to purchase is important and is now an evidence-based option.

CITATION(S): Timsina LR et al. National instant criminal background check and youth gun carrying. *Pediatrics* 2019 Dec 2; e20191071; [e-pub]. (https://doi.org/10.1542/peds.2019-1071)

Carter PM et al. Evidence to assess potential policy-oriented solutions for reducing adolescent firearm carriage. *Pediatrics* 2019 Dec 2; e20192334; [e-pub]. (https://doi.org/10.1542/peds.2019-2334)

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Eat Weight Disord 2019 Nov 28

Eating and Exercise Behaviors Among Collegiate Male Athletes

Competitive athletes were more likely to exercise when sick than their noncompetitive peers, and rates of eating pathology varied by sport.

There has been less research on the interplay between eating disordered behaviors and sports in young men compared with young women. Athletes, especially those who engage in sports where leanness may confer an advantage, are at high risk for dietary restricting behaviors.

Researchers distributed an online survey to 611 male Division I athletes (ages 18–26) at 10 colleges. Items focused on eating and weight control behaviors and motives for exercise. The researchers compared responses between competitive athletes (those actively competing in collegiate sports during the past year) and noncompetitive athletes (those engaged only in recreational exercise during the past year) and examined differences by sport type.

Competitive athletes were more likely than noncompetitive athletes to report exercising even when sick. Baseball players, cyclists, and wrestlers had the highest scores on the Eating Disorder Examination–Questionnaire (a validated tool), indicating eating pathology. Basketball players had the highest rate of binge eating (50%). Wrestlers were the most likely to report self-driven exercise for the purpose of influencing weight or body shape (57%).

COMMENT: Similar to findings in female athletes, this study showed different reasons for exercise among competitive and noncompetitive male collegiate athletes. Although the prevalence of restricted eating and eating disorders remains higher in young women, these data show that pediatricians should query male patients, especially elite athletes, about attitudes and behaviors that might represent eating pathology.

CITATION(S): Gorrell S et al. Eating behavior and reasons for exercise among competitive collegiate male athletes. *Eat Weight Disord* 2019 Nov 28; [e-pub]. (https://doi.org/10.1007/s40519-019-00819-0)

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N Engl J Med 2019 Dec 5; 381:2230

Ubrogepant: An Emerging Option for Acute Treatment of Migraine

Ubrogepant, a novel small-molecule CGRP receptor antagonist, shows promise as an option for the treatment of migraine attacks. Longer-term efficacy and safety data will be welcome.

Safe and effective treatments for migraine attacks remain an unmet need for many patients due to inadequate efficacy, contraindications, and tolerability issues. In particular, triptans, the current gold standard treatment for attacks, are contraindicated in patients with cardiovascular disease. Gepants are investigational small-molecule calcitonin gene–related peptide (CGRP) receptor antagonists that demonstrated efficacy in treating migraine attacks in proof-of-concept studies. Two manufacturer-funded, double-blinded, placebo-controlled phase 3 trials enrolling people with migraine with and without aura have now been conducted to evaluate the efficacy and safety of an oral formulation of ubrogepant in treating a single migraine attack.

In ACHIEVE I, Dodick and colleagues assigned 1672 people with 2 to 8 migraines per month to receive placebo or ubrogepant (50 mg or 100 mg). The primary endpoints were met: Significantly greater rates of pain freedom at 2 hours (PF-2H) were achieved with either 50 mg or 100 mg of ubrogepant than with placebo (PF-2H rates, 19.2%, 21.2%, and 11.8%, respectively). The absence of the most bothersome migraine-associated symptom (MBS; photophobia, phonophobia, or nausea) at 2 hours was significantly greater with 50 mg or 100 mg of ubrogepant than with placebo (38.6%, 37.7%, and 27.8%, respectively).

In ACHIEVE II, the researchers randomized 1686 patients with 2 to 8 migraines per month to receive placebo or ubrogepant (25 mg or 50 mg). PF-2H rates were significantly greater with either 25 mg or 50 mg of ubrogepant than with placebo (20.7%, 21.8%, and 14.3%, respectively). Absence of the MBS at 2 hours was statistically superior to placebo with only the 50-mg dose (38.9% vs. 27.4%).

The most common adverse events reported within 48 hours of treatment were experienced in <5% of participants in both trials. In ACHIEVE I these were nausea, somnolence, and dry mouth; in ACHIEVE II they were nausea and dizziness. Neither study had any signal for hepatotoxicity.

COMMENT: These demonstrate the efficacy and safety of ubrogepant for migraine acute treatment and lend support to CGRP receptor antagonism as a novel therapeutic mechanism. Important limitations are the single-attack trial design, exclusion of patients with cardiovascular contraindications, and lack of an active comparator. Further studies are needed to determine long-term safety and tolerability among unselected patient populations and to evaluate if ubrogepant is consistently effective across migraine attacks. Future head-to-head trials comparing ubrogepant with standard therapies would generate great interest, although they have practical imitations. Despite these uncertainties, ubrogepant is a promising alternative for patients who have tolerability issues with existing migraine-specific treatments.

Dr. Goadsby reports consulting for the manufacturer of ubrogepant. Dr. Ong is Consultant Neurologist and Clinical Lead for Headache Disorders, National University Health System, University Medicine Cluster, Department of Medicine, Division of Neurology, National University Hospital and Assistant Professor, Yong Loo-Lin School of Medicine, National University of Singapore.

CITATION(S): Dodick DW et al. Ubrogepant for the treatment of migraine. *N Engl J Med* 2019 Dec 5; 381:2230. (https://doi.org/10.1056/NEJMoa1813049)

Lipton RB et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: The ACHIEVE II randomized clinical trial. *JAMA* 2019 Nov 19; 322:1887. (https://doi.org/10.1001/jama.2019.16711)

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