

# Internal Medicine

Evidence-based summaries of the  
latest research in internal medicine

[ALERT]

## ABSTRACT & COMMENTARY

### Another Reason to Get the Flu Shot Every Year

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

**SYNOPSIS:** In a case-control study, among older adults, repeated vaccination for influenza was twice as effective in preventing severe influenza compared to non-severe influenza in patients who were admitted to the hospital.

**SOURCE:** Casado I, et al. Repeated influenza vaccination for preventing severe and fatal influenza infection in older adults: A multicentre case-control study. *CMAJ* 2018;190:E3-E12.

**A**lthough seasonal influenza can cause mild to severe illness, serious illness, including hospitalization and death, occurs more frequently among older adults. In fact, it has been established that during most seasons, people  $\geq 65$  years of age bear the greatest burden of severe influenza. For instance, it has been estimated in recent years that 71-85% of seasonal influenza-related deaths have occurred in people  $\geq 65$  years of age and 54-70% of seasonal influenza-related hospitalizations have occurred among people in that age group.<sup>1</sup> Based on data indicating that influenza vaccination programs produce a substantial health benefit in terms of averted cases, clinic visits, and hospitalizations, since 2010, the CDC and the

CDC's Advisory Committee on Immunization Practices (ACIP) has recommended routine annual influenza vaccinations for all persons aged  $\geq 6$  months who do not have contraindications.<sup>2</sup> While vaccine effectiveness can vary each season, recent studies show that influenza vaccination reduces the risk of illness by 40-60% among the overall population during seasons when most circulating influenza viruses are well-matched to the vaccine. For persons  $\geq 65$  years of age, any age-appropriate inactivated influenza vaccine formulation (standard-dose or high-dose, trivalent or quadrivalent, unadjuvanted or adjuvanted) or recombinant influenza vaccines are acceptable options. ACIP makes no preferential recommendation for any specific vaccine

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## Internal Medicine Alert

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product.<sup>3</sup> With aging, several factors may interfere with a robust vaccine response in older adults, including the effects of immunosenescence and concomitant major chronic conditions. However, recent data demonstrate that vaccination might reduce the severity of illness among people who are vaccinated but still become ill, including reduced deaths, ICU admissions, ICU length of stay, and overall duration of hospitalization among hospitalized influenza patients, especially among patients  $\geq 65$  years of age.<sup>4</sup> But while influenza vaccination in previous seasons may retain some preventive effectiveness, there is a lack of data on the effectiveness of repeated influenza vaccination in averting severe influenza in the elderly.

Casado et al conducted a case-control study during the 2013-14 and 2014-15 influenza seasons to assess the effectiveness of vaccination in preventing influenza among community-dwelling adults (age  $\geq 65$  years) who were admitted to one of 20 hospitals in Spain for laboratory-confirmed influenza (130 inpatients with severe influenza and 598 inpatients with non-severe influenza). Cases were matched with inpatient controls by sex, age, hospital, and admission date. Researchers compared vaccinated patients with patients who were unvaccinated in the current and previous three seasons. The adjusted effectiveness vaccination in the current and any previous season was 31% (95% confidence interval [CI], 13-46%) in preventing admission to the hospital for non-severe influenza, 74% (95% CI, 42-88%) in preventing admissions to the ICU, and 70% (95% CI, 34-87%) in preventing death. There was no significant effect on cases of severe influenza for vaccination in the current season only. Among inpatients with influenza, vaccination in the current and any previous season reduced the risk of severe outcomes (adjusted odds ratio, 0.45; 95% CI, 0.26-0.76).

## ■ COMMENTARY

The overall effect of seasonal influenza can vary from year to year and is based on several factors, including match of the vaccine strains to the circulating viruses. However, it is clear that influenza places a substantial burden on people's health and the U.S. economy each year. The CDC estimates that influenza has resulted in between 9.2 million and 35.6 million illnesses, between 140,000 and 710,000 hospitalizations, and between 12,000 and 56,000 deaths annually since 2010, with the elderly bearing the highest burden.<sup>5</sup> Casado et al demonstrated that repeated vaccination for seasonal influenza in older adults may be highly effective in preventing severe and fatal infection caused by influenza. As this was observed mainly in patients who were vaccinated in both the current and previous seasons, the study clearly highlights another reason for annual influenza vaccination in older adults, thus reinforcing the existing ACIP recommendation. ■

## REFERENCES

1. Kostova D, et al. Influenza illness and hospitalizations averted by influenza vaccination in the United States, 2005-2011. *PLoS One* 2013;8:e66312.
2. Fiore AE, et al. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010;59:1-62.
3. Grohskopf LA, et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the advisory committee on immunization practices — United States, 2017-18 influenza season. *MMWR Recomm Rep* 2017;66:1-20.
4. Anriola C, et al. Influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. *Clin Infect Dis* 2017;65:1289-1297.
5. Rolfes MA, et al. Annual estimates of the burden of seasonal influenza in the United States: A tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses* 2018;12:132-137.

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## ABSTRACT & COMMENTARY

# Physician Burnout: A Multi-specialty Perspective

By *Ellen Feldman, MD*

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

**SYNOPSIS:** Although different specialties address the problem of physician burnout, studies suggest the most effect is gained from organizational interventions.

**SOURCES:** Holoshitz N, Wann S. Burnout — There's an app for that. Helping physicians deal with job-related stress. *JAMA Cardiol* 2017; Jun. 14. doi: 10.1001/jamacardio.2017.1758. [Epub ahead of print].

Panagioti M, et al. Controlled interventions to reduce burnout in physicians: A systematic review and meta-analysis. *JAMA Intern Med* 2017;177:195-205.

Lacy B, Chan J. Physician burnout: The hidden health care crisis. *Clin Gastroenterol Hepatol* 2017; Jun. 30. <http://dx.doi.org/10.1016/j.cgh.2017.06.043>.

In 2015, the International Classification of Diseases, 10th revision (ICD-10) “elevated” burnout to a billable diagnosis.<sup>1</sup> Burnout — a syndrome developed in response to workplace stressors and often characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment — is not unique to the medical profession.<sup>2</sup> Yet, well before ICD-10, the medical world recognized a growing need for studies of physician burnout; the effect of this insidious condition on the individual provider, family members, patients, the healthcare team, and the healthcare system carries too many implications to ignore.

### A BRIEF HISTORICAL PERSPECTIVE

Drug addicts in treatment who stared at a cigarette until it “burned out” prompted psychologist Herbert Freudenberg, working with this population in the mid-1970s, to coin the term “burnout.” In his research and writings, he applied the term to a phenomenon he observed among his colleagues and staff members who exhibited a slow but steady decline in energy, motivation, and commitment to the job, as well as emotional depletion over time.<sup>3</sup>

Maslach and Johnson extended the work of Freudenberg and, in the 1980s, developed a scale to measure degree and effect of burnout. Notably, the Maslach Burnout Inventory (MBI) remains in use today as one of the few validated tools to measure this state. The team was the first to describe burnout as an all-encompassing phenomenon involving emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment stemming from the weight of professional stressors and responsibilities.<sup>4</sup> Although the scientific literature did not identify burnout until the 1970s, there is evidence that the syndrome existed well before that time. For example, when viewed through the lens of 2017, a 1953

published case study of a psychiatric nurse diagnosed with “exhaustion reaction” would qualify for a burnout diagnosis.<sup>5</sup> Popular literature also hints that burnout existed as far back as the turn of the 19th century, with progressive mental exhaustion, disillusionment, and loss of drive plaguing a protagonist in Thomas Mann’s 1901 *Buddenbrooks* (revived as a 2008 movie).<sup>3</sup>

The bulk of empirical studies in this field began in the 1980s with the development of research-validated tools. By the turn of the 20th century, articles describing “doctor discontent” and low morale pointed to a growth of burnout in the medical profession, with physician satisfaction declining from 1986 to 1997.<sup>6</sup> In response to this problem, in 2001, The Joint Commission mandated that all hospitals create a policy to address the well-being of physicians (distinct from disciplinary processes).<sup>7</sup> In 2015, Shanafelt et al published data regarding burnout collected in 2014 from 6,880 U.S. physicians and compared the results to a similar survey from 2011.

There was a significant increase in reports of burnout among U.S. physicians — 45.4% in 2011 to 54.4 % in 2014 ( $P < 0.001$ ); this trend was consistent across 24 specialties.<sup>8</sup> In a 2017 survey of a national sample of family physicians, Rassolian et al noted workplace factors frequently associated with physicians self-identifying as “burnt out” included the time burden of electronic medical record documentation (especially time spent at home), a hectic pace, and a chaotic work environment.<sup>9</sup>

### WHERE ARE WE NOW?

The number of articles and studies published regarding burnout in physicians has increased recently. The three selected for review here represent different perspectives across the broad field of medicine. In “Burnout — There’s an App for That,” an opinion piece in *JAMA*

*Cardiology*, Holoshitz et al emphasized the consequences of burnout, such as higher rates of drug and alcohol abuse in physicians with burnout and the association with depression and suicide. They urged readers to consider mindful meditation or, acknowledging the difficulty of finding time during a busy day, to download a mindfulness app for both instruction and practice of this technique. They cited a Cochrane database study associating mindfulness with improvement in burnout scores among hospital practitioners as well as primary care providers.

Holoshitz et al noted, “Empathy, membership in a caring community of peers, and a balanced lifestyle are central to countering burnout.” Furthermore, they recommended a change in the relationship between healthcare providers and healthcare institutions. They believe such a change should move in a direction to encourage institutions to support individuals in efforts to adjust work schedules, work intensity, and achieve a true work-life equilibrium.

In “Physician Burnout: The Hidden Health Care Crisis,” gastroenterologists Lacy et al presented a case study of a young gastroenterologist with burnout and reviewed the relevant literature discussing risk factors, causes, and treatment. They applied the characteristics of burnout — emotional exhaustion, depersonalization, and a reduced sense of personal accomplishment — to physicians specifically. They noted that a physician with emotional exhaustion may be depleted of compassion, that depersonalization may lead to detachment, and that a decreased sense of personal accomplishment leaves many feeling less able to complete tasks and less satisfied with patient care.

This team also emphasized prevention, noting that self-awareness regarding the potential for burnout is the first step in prevention. They encouraged physicians to practice self-care, sleep, exercise, and learn to “say no.” When discussing prevention and treatment, they emphasized literature support for organizational interventions, including leadership efforts to create a positive work environment that allows physicians some autonomy and encourages balance, rather than simply filling schedules with more tasks and/or patient time.

In an article in *JAMA Internal Medicine*, Panagioti et al presented a meta-analysis of studies regarding interventions to address burnout in physicians. They included 19 studies incorporating 1,550 physicians. They identified three main objectives in their study: 1) Assess the effectiveness of interventions to reduce the development of physician burnout; 2) Assess which type of intervention — organizational or individual — is more effective; and 3) Assess if the experience of the physician or type of healthcare setting affects the effectiveness of the intervention.

## SELECTED RESULTS

Results were interpreted using standardized mean difference (SMD) — a useful measure when comparing multiple studies with a variety of interventions. Sometimes used interchangeably with “treatment effect,” a negative SMD in this case indicates the degree to which treatment is more effective than control. The following guidelines help interpret the magnitude of effect: SMD = 0.2 (small); SMD = 0.5 (medium); SMD = 0.8 (large).<sup>9</sup>

Based on these results and their analysis, Panagioti et al concluded that interventions for burnout in physicians showed evidence of efficacy (“small significant” reduction in burnout.) More specifically, this group noted that organizational-directed interventions produce higher treatment effects than physician-directed interventions, and that the most impact has been shown when experienced physicians are involved and when interventions are performed in primary care settings.

These articles demonstrate different approaches to physician burnout: an editorial promoting self-care; a literature review promoting prevention; and a meta-analysis suggesting that organizational interventions are most effective in combating burnout, but that individual physician effort at self-regulation and mind-body techniques can be effective. Although these articles limited subjects to physicians, the evidence is mounting that advanced practice practitioners are at risk for burnout as well.<sup>10</sup> There is little doubt that rigorous, large-scale studies are necessary to further illuminate the path of burnout prevention and recovery. In the interim, perhaps the most significant takeaway message for all practitioners includes the following:

1. Be aware of the potential hazards of burnout; think about preventive efforts early in your career.
2. Consider “practicing what you preach” in terms of self-care — make time for exercise, eat well, socialize, and practice mindfulness or self-awareness.
3. Actively intervene to remind health organizations that initiatives to encourage a healthy work-life balance among all providers will provide benefit to many — not only the individual provider, but also patients and the entire healthcare system. Remind administrators of the financial implications associated with burned-out providers (resulting from potential increases in poor patient satisfaction ratings, high provider turnover, and early retirement, for example). Work together with practitioners in your own organization to “speak with one voice” to emphasize the importance of preventing and fighting burnout.
4. Speak for implementing practical and concrete interventions, such as decreased workloads, reduction of repetitive non-technical tasks, and adjusting work hours to allow time for personal growth and development.

Few of us imagined our lives as physicians would involve struggling with issues of burnout; most entering the profession expect a fulfilling professional career in concert with a satisfying family and social life. Yet the staggering reality of burnout growth in physicians tells another story. Learning to guard against burnout can help all providers accept the importance of shaping a professional lifestyle that involves elements of moderation, self-reflection, and self-awareness. Just as the simple act of hand washing carries critical importance in the complex issue of infection control, developing a basic habit of self-care, including an expectation that provider self-care will be supported actively by healthcare organizations, can become key in stemming the growth of burnout in our profession. ■

#### REFERENCES

1. ICD10Data.com. Available at: <http://bit.ly/2G0Gog3>. Accessed Aug. 21, 2017.
2. PubMed Health. Depression: What is burnout? Available at: <http://bit.ly/2fh7gV5>. Accessed Aug. 10, 2017.
3. Maslach C, Schaufeli WB. Historical and conceptual development of burnout. Available at: <http://bit.ly/2FgsOwF>. Accessed Aug. 10, 2017.
4. Maslach C, Leiter MP. Understanding the burnout experience: Recent research and its implications for psychiatry. *World Psychiatry* 2016;15:103-111.
5. Muheim F. Burnout: *History of a Phenomenon*. *Burnout for Experts*. New York: Springer Science+Business Media; 2013: 37-46.
6. Spickard A Jr, et al. Mid-career burnout in generalist and specialist physicians. *JAMA* 2002;288:1447-1450.
7. Spickard A. What do we know about physician well-being? *West J Med* 2001;174:23-24.
8. Shanafelt TD, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. *Arch Intern Med* 2012;172:1377-1385.
9. Rassolian M, et al. Workplace factors associated with burnout of family physicians. *JAMA Intern Med* 2017;177:1036-1038.
10. Waddimba AC, et al. Predictors of burnout among physicians and advanced-practice clinicians in central New York. *J Hosp Admin* 2015;4:6.
11. Faraone SV. Interpreting estimates of treatment effects: Implications for managed care. *P T* 2008;33:700-711.

## BRIEF REPORT

# Providers Facilitate Transmission of Resistant Organisms

By Carol A. Kemper, MD, FACP

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Dr. Kemper discloses no financial relationships relevant to this field of study.

SOURCE: Grabowski ME, et al. Provider role in transmission of carbapenem-resistant *Enterobacteriaceae*. *Infect Control Hosp Epidemiol* 2017;38:1329-1334.

Grabowski et al investigated the provider role in patient-to-patient transmission of carbapenem-resistant *Enterobacteriaceae* (CRE) in a hospital facility with a robust CRE surveillance program. Between 2011 and 2015, researchers conducted a case-controlled study of patients who acquired CRE during their hospitalization and those who did not. Cases demonstrated negative stool CRE surveillance within 48 hours of admission, with a subsequent positive CRE culture, and a hospital stay of at least nine days.

Controls had two or more negative stool surveillance studies with a similar length of hospital stay (LOS). Patient-provider interactions were documented per day. CRE status was documented in the electronic record, and any patient with a history of CRE was placed in contact isolation with use of gowns and gloves. Hand hygiene was monitored actively, and compliance with hand hygiene was 81%. A total of 121 patients acquired

CRE during their hospital stay during the six-year study period. Cases were admitted more commonly to the general surgery/transplant unit, ICU, or burn unit. The median LOS for cases was 49 days compared with 20.5 days for controls. Cases experienced an average  $43 \pm 8$  unique documented provider interactions in one week (an average of  $10.5 \pm 3$  per day) compared with  $41 \pm 8.7$  for controls (an average of  $9.5 \pm 3$  per day).

Case patients were statistically significantly more likely to be cared for by a CRE-shared provider, meaning providers caring for another patient with CRE, than controls. Case patients saw an average of four more shared providers per week than controls. Controlling for age and ICU stay, the odds of a case being exposed to a shared-source provider was 2.27 higher than for controls. Providers caring for a known CRE patient appear to play an active role in patient-to-patient transmission. ■

# Apalutamide Tablets (Erleada)

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

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

The FDA has approved the first treatment for non-metastatic, castration-resistant prostate cancer (NM-CRPC). Apalutamide is a second-generation nonsteroidal androgen receptor inhibitor. Currently approved androgen receptor inhibitors (e.g., bicalutamide, enzalutamide) are approved for metastatic prostate cancer. Apalutamide demonstrates high affinity to the androgen receptor and favorable activity in CRPC xenograft models.<sup>1,2</sup> The FDA granted the treatment priority review. It is marketed as Erleada.

## INDICATIONS

Apalutamide is indicated for the treatment of patients with NM-CRPC.<sup>3</sup>

## DOSAGE

The recommended dose is 240 mg (four 60 mg tablets) orally once daily.<sup>3</sup> It may be taken without regard to meals. Patients also should receive a gonadotropin-releasing hormone analog (e.g., leuprolide, goserelin) concurrently or should have undergone bilateral orchiectomy. Apalutamide is available as 60 mg tablets.

## POTENTIAL ADVANTAGES

Apalutamide is the first FDA-approved treatment for NM-CRPC.

## POTENTIAL DISADVANTAGES

Fall and fractures have been associated with apalutamide (falls: 16% for apalutamide vs. 9% for placebo; fractures: 12% for apalutamide vs. 7% for fractures).<sup>3</sup> Other adverse reactions include fatigue, arthralgia, rash, and hypothyroidism.<sup>1,2</sup> Two subjects developed a seizure (0.2%) in the clinical trial, compared to none in the placebo group.

## COMMENTS

Efficacy and safety of apalutamide were evaluated in a double-blind, randomized, placebo-controlled trial in subjects with NM-CRPC (Selective Prostate Androgen Receptor Targeting with ARN-509).<sup>3,4</sup> Subjects were at high risk for development of metastasis and exhibited local or regional node disease (class N0) or presented with malignant pelvic lymph nodes that measured < 2 cm in the short axis (N1) and were located below the aortic bifurcation. Androgen-deprivation therapy continued throughout the trial. Subjects were randomized 2:1 to apalutamide (240 mg daily; n = 806) or placebo (n = 401). The primary efficacy endpoint was time to first

detection of metastasis (metastasis-free survival) or death from any cause. Subjects were stratified by Prostate Specific Antigen (PSA) Doubling Time ( $\leq 6$  months or > 6 months), use of bone-sparing agents, and locoregional disease. Median metastatic-free survival was 40.5 months for apalutamide vs. 16.2 months for placebo (hazard ratio, 0.28; 95% confidence interval, 0.23-0.35). The benefit was seen across the different subgroups (e.g., high PSA levels, short PSA doubling time, or local or regional nodal disease at baseline). In addition, there was significant improvement in time to metastasis, progression-free survival, and time to symptomatic progression. Data were not mature enough to estimate overall survival.

## CLINICAL IMPLICATIONS

Prostate cancer is the second most commonly diagnosed cancer in men and is the second leading cause of cancer death among American men.<sup>5</sup> Chemical or surgical castration is an effective treatment for castration-sensitive disease; however, 10-20% of prostate cancers are castration-resistant, and among those patients, about 16% show no evidence of metastatic disease at the time of castration-resistant diagnosis. CRPC progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (< 50 ng/dL).<sup>6</sup> Apalutamide offers a potentially promising new oral option for NM-CRPC at high risk for metastasis. Although survival benefit has not been demonstrated, the FDA approved the drug using a new endpoint of “median metastasis-free survival.” More data from SPARTAN and further studies will demonstrate whether this translates to survival benefit. The cost of apalutamide is \$10,920 for a 30-day supply. ■

## REFERENCES

1. Cancian M, Renzulli JF 2nd. Nonmetastatic castration-resistant prostate cancer: A modern perspective. *Urology* 2018 Jan 31. pii: S0090-4295(18)30044-X. doi: 10.1016/j.urology.2018.01.010. [Epub ahead of print].
2. Clegg NJ, et al. ARN-509: A novel antiandrogen for prostate cancer treatment. *Cancer Res* 2012;72:1494-1503.
3. Erleada Prescribing Information. Janssen Products, LP, February 2018.
4. Smith MR, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018 Feb 8. doi: 10.1056/NEJMoa1715546. [Epub ahead of print].
5. Luo J, et al. Treatment of nonmetastatic castration-resistant prostate cancer. *Oncology (Williston Park)* 2016;30:336-344.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Feb. 14, 2018. Available at: <http://bit.ly/2lexEgW>. Accessed March 8, 2018.

## Cardiovascular Benefits of Pharmacotherapies for Type 2 Diabetes

SOURCE: Yandrapalli S, et al. Cardiovascular benefits and safety of non-insulin medications used in the treatment of type 2 diabetes mellitus. *Postgrad Med* 2017;129:811-821.

The primary goals of diabetes management are reductions in microvascular endpoints (retinopathy, neuropathy, nephropathy), macrovascular endpoints (myocardial infarction, stroke), and improved quality of life (less dry mouth, urinary frequency, visual disturbance). In the most recent decade, the FDA has mandated that new pharmacologic entities for management of glucose in type 2 diabetes (T2DM) establish cardiovascular (CV) safety with a substantial clinical trial. As a result, there are now several agents that have shown not only CV safety in T2DM, but also actual reductions in CV endpoints.

The three agents with FDA labeling for CV risk reduction based on their successful clinical trials are empagliflozin (EMPA-REG), canagliflozin (CANVAS), and liraglutide (LEADER). Another glucagon-like peptide-1 receptor agonist, semaglutide, has been approved for treatment of T2DM. It demonstrated CV risk reduction in a recent clinical trial (SUSTAIN), but does not yet carry FDA labeling for CV risk reduction.

The most recent American Diabetes Association 2018 guidance for pharmacotherapy of T2DM suggests that for patients with existing CV disease who are uncontrolled on metformin and lifestyle, consideration should be given to prioritizing agents demonstrated to provide CV risk reduction (empagliflozin, liraglutide, and canagliflozin). ■

## The Vagaries of Reported Penicillin Allergy

SOURCE: Sundquist BK, et al. Proactive penicillin allergy testing in primary care patients labeled as allergic: Outcomes and barriers. *Postgrad Med* 2017;129:915-920.

I am allergic to penicillin, or at least that's what I say in healthcare settings when someone asks. My designation as penicillin allergic occurred around age 5 when I developed a rash after a shot of penicillin. The malady I was suffering was called "a respiratory infection," with the subsequent all-encompassing remedy supplied: a shot of penicillin (at least that's how it was in 1951). I am told that within the next day or two I developed a rash, and was told to eschew penicillin.

But was I really allergic? Certainly, there are many commonplace viral upper respiratory illnesses afflicting youngsters that can manifest a rash. Subsequently, I have received cephalosporins uneventfully. The literature says that > 90% of patients who report a history of penicillin allergy can tolerate penicillin. Unstimulated penicillin sensitivity wanes over time: By age 10 years, 80% of allergic subjects are no longer allergic.

Sundquist et al recruited patients with a history of penicillin allergy. Skin testing in 37 subjects (prick testing and intradermal testing) identified *none* as allergic; subsequent oral challenge also demonstrated *no* positive results. The authors suggested that good antibiotic stewardship supports consideration of clarification of whether patients who report penicillin allergy are allergic. Numerous infectious diseases are best served by penicillin treatment for the sake of cost considerations, specificity, and antibiotic stewardship. ■

## Osteoblast Modulation in Osteoporosis Treatment

SOURCE: Corrado A, et al. Osteoblast as a target of anti-osteoporotic treatment. *Postgrad Med* 2017;129:858-865.

In healthy bones, osteoclast activity is balanced with osteoblast activity to produce a continuing stream of freshly created bone by degradation of aging bone and replacement with new bone. After attainment of the peak level of mature bone in early adulthood, osteoclast activity modestly exceeds osteoblast activity, leading to a gradual decline in bone mineral density that we call age-related bone loss to distinguish it from the more rapid bone loss seen at menopause (regardless of age) due to estrogen loss that characteristically outpaces simple age-related bone loss.

Most pharmacologic interventions currently in use for treatment or prevention of osteoporosis rely on osteoclast inhibition to enhance (or at least maintain) bone mineral density. In contrast, teriparatide primarily works by stimulation of osteoblasts. Estrogen also produces some positive activity on osteoblasts, such as inhibition of osteoblast apoptosis. Finally, even though the primary mechanism of bisphosphonates is inhibition of osteoclastic activity, even this pharmacologic class produces some favorable effects on osteoblasts.

One additional class of pharmacologic agent has shown promising effects: The anti-sclerostin antibody agent romosozumab provides both stimulation to osteoblasts and diminution of osteoclast activity. This agent is pending FDA approval. ■

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## CME QUESTIONS

1. Based on the results of the study by Casado et al, which of the following is the best strategy for preventing severe and fatal infection caused by seasonal influenza in older adults?
  - a. Repeated annual vaccination
  - b. One-time vaccination
  - c. Biennial vaccination
  - d. Triennial vaccination
2. Which of the following is *true* about physician burnout?
  - a. There are few controlled studies and conflicting results regarding appropriate interventions; the best recommendation at this point is careful monitoring.
  - b. Recent studies show it is affecting more providers, and although there needs to be more rigorous investigations, organizational modifications, such as scheduling changes as well as individual self-care, are essential to prevention and intervention.
  - c. It is less common among more experienced physicians, perhaps because burned out physicians leave the profession or retire early.
  - d. It is a popular “trendy” diagnosis with little empirical evidence or studies even documenting the existence of burnout as a true phenomenon.

## CME OBJECTIVES

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

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

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