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Evidence-based summaries of the latest research in internal medicine

ABSTRACT & COMMENTARY

Too Much of a Good Thing

By Seema Gupta, MD, MSPH

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

SYNOPSIS: In the United States in 2010 and 2011, an estimated 30% of outpatient oral antibiotic prescriptions may have been inappropriate, a finding that supports the need for establishing a goal for outpatient antibiotic stewardship.

SOURCE: Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among U.S. ambulatory care visits, 2010-2011. *JAMA* 2016;315:1864-1873.

Antimicrobials are perhaps one of the most successful forms of chemotherapy in the history of medicine. Since their discovery in the early 1900s, antibiotics have contributed significantly to the control of communicable diseases that have been the leading causes of human morbidity and mortality throughout human history. However, as their popularity and utilization expanded, antibiotic resistance has become a significant public health issue, both in the United States and across the world, potentially creating infectious diseases that may become unresponsive to antibiotic treatments.

In the United States, at least 2 million people become infected with antibiotic-resistant bacteria, and at least 23,000 people die each year as a direct result of these infections.[1] According to the CDC, antibiotic resistance in the United States costs an estimated $20 billion a year in excess healthcare costs, $35 billion in other societal costs, and results in more than 8 million additional days in the hospital. The primary driver of antibiotic resistance is the overuse and misuse of antibiotics. In 2011, healthcare providers prescribed 262 million courses of antibiotics, equating to more than five prescriptions written for every six residents.[2] It is also estimated that approximately 50% of antibiotic prescriptions written in the outpatient setting and 30-50% of antibiotics prescribed in hospitals may be unnecessary or inappropriate.[3] Therefore, decreasing inappropriate use is essential to reducing both antibiotic resistance and adverse events.

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Despite the release of a national action plan for combating antibiotic-resistant bacteria that sets a target of reducing inappropriate antibiotic use in the outpatient setting by 50% by 2020, the precise degree to which antibiotic use is inappropriate and amenable to reduction is unknown.[4] Additionally, previous goals and measures for the appropriate use of antibiotics have focused on targeted, specific age groups and conditions.

Fleming-Dutra et al established a baseline of the current rate of outpatient, oral antibiotic prescriptions by age and diagnosis and estimated the overall rate of appropriate, outpatient antibiotic prescriptions in the United States.

Using the 2010-2011 data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, researchers estimated the baseline annual numbers and population-adjusted rates with 95% confidence intervals (CI) of ambulatory visits with oral antibiotic prescriptions in the United States by age, region, and diagnosis. Researchers found that in 2010 and 2011, of the 184,032 sampled ambulatory care visits, 12.6% of visits (95% CI, 12%-13.3%) resulted in antibiotic prescriptions, with an estimated 506 antibiotic prescriptions (95% CI, 458-554) per 1,000 population annually. The number of antibiotic prescriptions varied geographically across the United States, ranging from 423 antibiotic prescriptions (95% CI, 343-504) in the West to 553 antibiotic prescriptions (95% CI, 459-648) in the South, per 1,000 population. The annual antibiotic prescription rate was found to be highest among children younger than two years of age at 1,287 antibiotic prescriptions (95% CI, 1,085-1,489) per 1,000 population.

Sinusitis was the diagnosis associated with the most antibiotic prescriptions per 1,000 population (56 antibiotic prescriptions [95% CI, 48-64]), followed by suppurative otitis media (47 antibiotic prescriptions [95% CI, 41-54]), and pharyngitis (43 antibiotic prescriptions [95% CI, 38-49]). Overall, acute respiratory conditions per 1,000 population led to 221 antibiotic prescriptions (95% CI, 198-245) annually, but only 111 antibiotic prescriptions were estimated to be appropriate for these conditions. Researchers also found that among all conditions and ages combined in 2010 and 2011, an estimated 506 antibiotic prescriptions (95% CI, 458-554) per 1,000 population were written annually, and, of these, only 353 antibiotic prescriptions were estimated to be appropriate.

■ COMMENTARY

In the United States, an estimated 154 million prescriptions for antibiotics were written in ambulatory care settings annually from 2010-2011. In this study, researchers found that almost half of antibiotic prescriptions for acute respiratory conditions may have been unnecessary, representing 34 million antibiotic prescriptions annually. It is even more astounding to consider that collectively, across all conditions, an estimated 30% of outpatient, oral antibiotic prescriptions may have been inappropriate, although this is likely a conservative estimate. Although these findings offer a critical starting point to understand prescribing practices in the ambulatory care setting, it is equally vital that clinicians consider national, regional, and local approaches to address this challenge in view of geographic variances. However, there will be some elements common to all strategies, which include altering clinician behavior and practice culture as well as educating patients and families regarding the role of antibiotics in medical care.

The Fleming-Dutra et al study also establishes baseline estimates about outpatient antibiotic prescribing. Targeting interventions at both clinician and patient/community levels would enable reaching the national goal of reducing outpatient antibiotic use by 50% by 2020. As there are a number of antibiotic stewardship activities ongoing in outpatient settings across the nation, it is critical clinicians do their part to ensure appropriate antibiotic prescribing. This includes a consideration of displaying informational posters in patient waiting rooms to encourage active conversations around the need for antibiotics. Studies demonstrate most patients will be satisfied without antibiotics if physicians communicate why an

antibiotic is unnecessary, what patients can do to feel better, what to expect with their illnesses, and when they should return if they are not improving or are getting worse.[5] After all, antibiotic resistance is one of the most urgent public health threats of our time, and by rethinking each time we consider prescribing an antibiotic, we can treat patients appropriately while sustaining the efficacy of existing agents. ■

REFERENCES

1. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Available at: http://1.usa.gov/1s07BAF.
2. Hicks LA, Bartoces MG, Roberts RM, et al. U.S. outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis* 2015;60:1308-1316.
3. Shapiro DJ, Hicks LA, Pavia AT, et al. Antibiotic prescribing for adults in ambulatory care in the USA, 2007–09. *J Antimicrob Chemother* 2014;69:234-240.
4. National Action Plan for Combating Antibiotic-Resistant Bacteria. Available at: http://1.usa.gov/1yiurjQ.
5. Drekonja DM, Filice GA, Greer N, et al. Antimicrobial stewardship in outpatient settings: A systematic review. *Infect Control Hosp Epidemiol* 2015;36:142-152.

ABSTRACT & COMMENTARY

Predicting Seizure Recurrence with Routine EEG after First Unprovoked Seizure

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Pargeon reports no financial relationships relevant to this study.

SYNOPSIS: Using positive likelihood ratios, an adult and child with epileptiform discharges on electroencephalography were estimated to have a 77% and 66% probability, respectively, of recurrent seizures.

SOURCE: Bouma HK, Labos C, Gore GC, et al. The diagnostic accuracy of routine electroencephalography after a first unprovoked seizure. *Eur J Neurol* 2016;23:455-463.

Prior to 2014, the International League Against Epilepsy (ILAE) defined epilepsy as two or more unprovoked seizures separated by more than 24 hours; however, in 2014, the ILAE revised the definition and acknowledged circumstances in which a single unprovoked seizure may be diagnosed as epilepsy if the risk of seizure recurrence is ≥ 60% within the next 10 years.1 One way to assess risk is the routine electroencephalography (EEG), which per the last practice parameter, published in 2007, stated that epileptiform abnormalities after a first unprovoked seizure occur in about 23% of patients and are predictive of future recurrence.[2] Bouma et al updated previous reviews and meta-analyses of the predictive accuracy of routine EEG after a first unprovoked seizure using more rigorous guidelines for conducting and reporting reviews published in 2007 and 2009.

The authors systematically searched for prospective or retrospective cohort studies featuring patients of any age, presenting with a first unprovoked seizure who underwent a routine EEG, defined as lasting up to 60 minutes, and were followed for recurrence for a minimum of one year. A "positive" test was defined as the presence of epileptiform discharges. Other information recorded included seizure type, epilepsy etiology, any treatments with anti-epileptic drugs, timing of EEG relative to the seizure occurrence, and activation procedures. Two authors independently screened all titles and abstracts identified by the initial search (n = 3,096), of which 180 full texts were reviewed, yielding 15 studies.

Despite their systematic process for study selection, there was some heterogeneity between the 15 selected studies, which included 1,799 total participants, with some characteristics variably reported. For instance, in nine studies participants were primarily pediatric, with the remainder mostly a mixture of adult and pediatric populations. In seven studies, the duration of the EEG was not defined (described as "routine"). Also, in seven studies the timing of the EEG relative to the first seizure was not defined, and for the remaining eight studies there was a range from < 48 hours to several months.

The reported pooled risk of seizure recurrence after a first unprovoked seizure was 44.2%, with the overall pooled sensitivity and specificity for routine EEG of 44.5% and 79.6%, respectively. The pooled sensitivity for routine EEG for adults as compared to children, however, was significantly lower at 17.3% vs. 57.8%, whereas the pooled specificity trended higher in adults (94.7% vs. 69.6%). Positive and negative likelihood ratios were calculated for adults and children, which were used with Fagan nomograms

(assuming a pretest probability of 50%) to estimate post-test probabilities of epilepsy given a "positive" or "negative" test. They estimated an adult presenting with a first unprovoked seizure has a 77% post-test probability of recurrence if the routine EEG is positive and 47% if it is negative, whereas a child has a 66% post-test probability of recurrence with a positive test and 38% probability with a negative test. They were unable to conduct any other subgroup analyses given the heterogeneity of the data.

■ COMMENTARY

The 2014 revised ILAE definition of epilepsy, allowing for potential diagnosis after one unprovoked seizure in circumstances where there is at least a 60% chance of recurrence, emphasizes the need to know the diagnostic accuracy of tests, especially EEG. This was the primary goal of this study; however, as with all meta-analyses, it is sometimes difficult to answer specific questions when the source articles try answering others or are missing key pieces of information. For instance, a few studies included only "genetic" forms of epilepsy, whereas the majority were inclusive of those with either unknown causes or any etiology, which may affect the generalizability of these results. Additionally, for many of the studies, abnormal EEG was one of only many factors considered for future seizure recurrence, including presence of structural abnormalities, timing of first seizure, treatment with automated external defibrillators, and seizure type. Within a few individual studies, abnormal EEG was not a statistically significant variable related to recurrence. Further, while a majority of the studies reported either focal or generalized epileptiform discharges, several simply reported "abnormal" EEGs. Finally, the timing of EEG relative to the first seizure either was not reported or was highly variable across the included studies, but early EEG may be more likely to capture epileptiform discharges than a delayed study.[3] ■

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: A practical clinical definition of epilepsy. *Epilepsia* 2014;55:475-482.
2. Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review), report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2007;69:1996-2007.
3. King MA, Newton MR, Jackson GD, et al. Epileptology of the first-seizure presentation: A clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998;352:1007-1011.

ABSTRACT & COMMENTARY

Longer Course Therapy for Lyme Disease Is Not Beneficial

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports that he has received research support from Actavis.

SYNOPSIS: A randomized, placebo-controlled clinical trial from the Netherlands found that longer-term antibiotic therapy for Lyme disease did not improve health-related quality of life compared to a standard course of treatment.

SOURCE: Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *N Engl J Med* 2016;374:1209-1220.

Despite clear recommendations from national guidelines, the duration of therapy for Lyme disease is still debated. This is mostly due to the fact that a significant minority of patients with documented Lyme disease who were treated appropriately continues experiencing symptoms such as fatigue, pain, and neurological or cognitive dysfunction. Therefore, Dutch investigators asked whether longer course therapy would be beneficial in alleviating these symptoms.

The study was a randomized, double-blind trial conducted at two sites in the Netherlands. Patients were eligible to participate if they suffered from persistent symptoms attributed to Lyme disease after an erythema migrans rash or positive *Borrelia burgdorferi* IgG or IgM antibodies. All patients received open-label IV ceftriaxone for two weeks. They were then randomized to receive a 12-week course of doxycycline, clarithromycin plus hydroxychloroquine, or placebo. The primary outcome was health-related quality of life at the end of the treatment period, which was ascertained using the physical-component summary score of the RAND SF-36. The mean score of the SF-36 (± standard deviation) in the general population is 50 ± 10, with higher scores representing a better

quality of life. Secondary outcomes included physical and mental aspects of health-related quality of life, and fatigue.

A total of 280 patients started oral therapy after randomization: 86 received doxycycline, 96 received clarithromycin plus hydroxychloroquine, and 98 received placebo. There were no differences in adherence between the groups ($P = 0.50$). At 14 weeks, the SF-36 was 35 in the doxycycline group (95% confidence interval [CI], 33.5-36.5), 35.6 in the clarithromycin-hydroxychloroquine group (95% CI, 34.2-37.1), and 34.8 in the placebo group (95% CI, 33.4-36.2). Overall, there was no significant difference between the groups in the modified intention-to-treat analysis ($P = 0.69$). Furthermore, there were no significant differences in either of the secondary outcomes between the three groups. Overall, 205 patients reported at least one adverse event. Most of these were drug-related, with rash and diarrhea most common. Fourteen patients discontinued the randomized portion of the trial due to an adverse event; there was no significant difference among the three study groups in terms of adverse reactions.

■ COMMENTARY

The Berende et study adds to the mounting body of evidence that longer courses of antibiotics for Lyme disease are not beneficial. Two previous trials that also used IV ceftriaxone followed by oral doxycycline or placebo for 60 days found no significant differences between treatment groups. In the Berende et al study, the median duration of symptoms was 2.7 years in the two antibiotic groups and 2.1 years in the placebo group, yet 9-13% had not previously received antibiotic treatment. Twenty-eight percent of patients recalled an erythema migrans rash, while serology was positive in about two-thirds. This raises the possibility of false-positive results, especially since a Western blot assay was not performed, which is a routine procedure after serology in the United States. It is also worth noting that the species of *B. burgdorferi* present in the Netherlands manifests differently than the one in the United States, including a longer duration of initial illness. Finally, the high rate of adverse events observed in the study is a reminder that prolonged courses of antibiotics are not benign and have the potential for causing patient harm.

So what should a clinician tell a patient who had Lyme disease and continues to experience lingering symptoms such as fatigue and chronic joint pain? Basically, more antibiotics will not help and may instead lead to further complications. An accompanying editorial noted an interesting recent study that showed post-infectious cytokine and metabolic changes after Lyme disease that are not observed after other infections.[1] Further studies are warranted to determine if these post-infectious changes could somehow be modified and if doing so might lead to symptomatic improvement.

For now, it is important to screen for other medical conditions such as depression and endocrine disorders, such as diabetes mellitus and hypothyroidism, that might be treatable. Moreover, many of these patients suffer from insomnia, and improved sleep hygiene sometimes improves their quality of life. While it is often frustrating for patients to experience ongoing, unexplainable symptoms following Lyme disease, the strong evidence that antibiotics are not beneficial will hopefully encourage investigators to develop novel hypotheses that ultimately lead to a better understanding of this condition. ■

REFERENCE

1. Melia MT, Auwaerter PG. Time for a different approach to Lyme disease and long-term symptoms. *N Engl J Med* 2016;374:1277-1278.

PHARMACOLOGY UPDATE

Reslizumab Injection (Cinqair)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

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

A second monoclonal antibody targeting the interleukin-5 receptor has been approved for the maintenance treatment of severe asthma. Reslizumab follows mepolizumab (Nucala) and is marketed as Cinqair.

INDICATIONS

Reslizumab is indicated for add-on maintenance treatment of adult patients with severe asthma with eosinophilic phenotype.[1]

DOSAGE

The recommended dose is 3 mg/kg once every

four weeks by IV infusion over 20-50 minutes.[1] Reslizumab is available as 100 mg single-use 10 mL vials.

POTENTIAL ADVANTAGES

Reslizumab provides another option for the management of severe eosinophilic asthma.

POTENTIAL DISADVANTAGES

Reslizumab requires IV infusion, while mepolizumab is administered subcutaneously. The most common adverse event is the elevation of creatine phosphokinase (14% vs. 9% for placebo).[1] Anaphylaxis occurred in 0.3% of patients receiving the drug. Anti-reslizumab antibodies develop in 5.4% of subjects during treatment.

COMMENTS

Reslizumab is a humanized monoclonal antibody (IgG4, kappa) produced by recombinant DNA technology in murine myeloma cells. It is an interleukin-5 antagonist. The efficacy of reslizumab was evaluated in four randomized, double-blind, placebo-controlled studies. Two were 52-week studies (n = 953) and two were 16-week studies (n = 811).[1-5] Asthmatic subjects with an eosinophilic phenotype in the 52-week studies experienced at least one exacerbation requiring systemic corticosteroid use during the past 12 months and a blood eosinophil count of at least 400/mcL. Eighty-two percent received a medium-high dose inhaled steroid plus a long-acting beta agonist at baseline. Subjects were randomized to reslizumab 3 mg/kg every four weeks or 13 placebo doses. The primary endpoint was the frequency of asthma exacerbations, defined as a worsening of asthma that required use of 1) a systemic corticosteroid, 2) ≥ two-fold increase in the use of inhaled steroid for three or more days, or 3) an unscheduled visit to a healthcare provider (urgent treatment, ED visit, or hospital admission). Medical intervention was corroborated by decline in pulmonary function or worsening of clinical signs or symptoms. The annual rates of exacerbations in those treated with reslizumab declined 50-59% and those requiring hospitalization or ED visits by about one-third. A significantly higher proportion of the reslizumab group did not have an exacerbation by week 52 (62% and 75%) compared to 46-55% in the placebo group. Lung function (change in FEV_1) was evaluated in all four studies and was the primary endpoint in the two 16-week studies. The second 16-week study did not require a minimum blood eosinophil count. This study evaluated the relationship between treatment effect and blood eosinophil counts. Change in FEV_1 ranged from 93 mL to 160 mL for the first three studies and 76 mL for the fourth study. Researchers found no association between baseline eosinophil counts and treatment. Responses (≥ 0.5-point improvement) to the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaires were all numerically higher for reslizumab for the three studies. The difference between reslizumab and placebo was modest, as there was statistical difference for both questionnaires for one study and only one for the third study.[2] A small study (n = 106) suggested patients with higher ACQ scores and nasal polyposis may show greater benefit.[6]

CLINICAL IMPLICATIONS

Eosinophilic asthma is a phenotype of asthma characterized by high eosinophil count in the blood, lung, and sputum. It is postulated that interleukin-5 is the key mediator of eosinophilic asthma.[7] Reslizumab is the second monoclonal antibody interleukin-5 antagonist after mepolizumab. Currently, there are no direct comparisons between these two drugs. Both have been reported to reduce exacerbations about 50%; however, mepolizumab reduces oral corticosteroid use, but reslizumab appeared to show a numerically better improvement in lung function in clinical trials when compared across studies.[1,8] The cost for mepolizumab 100 mg is $2,500. Reslizumab dose is weight-based at 3 mg/kg, requiring two vials for a 66 kg patient ($1,670) and three vials for patients 67 kg-100 kg ($2,505). ■

REFERENCES

1. Cinqair Prescribing Information. Teva Pharmaceuticals. March 2016.
2. FDA. Center for Drug Evaluation and Research, Application Number 761033Orig1s000, Summary Review. Available at: http://1.usa.gov/1sgzcOU. Accessed May 10, 2016.
3. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-366.
4. Bjermer L, Lemiere C, Maspero J, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: A randomized phase 3 study. *Chest* 2016 Apr 4. pii: S0012-3692(16)47551-3. doi: 10.1016/j.chest.2016.03.032. [Epub ahead of print].
5. Corren J, Weinstein S, Janka L, et al. Phase 3 study of reslizumab in patients with poorly controlled asthma: Effects across a broad range of eosinophil counts. *Chest* 2016 Mar 24. pii: S0012-3692(16)45715-6. doi: 10.1016/j.chest.2016.03.018. [Epub ahead of print].
6. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: A randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011;184:1125-1132.
7. Varricchi G, Bagnasco D, Borriello F, et al. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: Evidence and unmet needs. *Curr Opin Allergy Clin Immunol* 2016;16:186-200.
8. Nucala Prescribing Information. GlaxoSmithKline. November 2015.

Clinical Briefs

By Louis Kuritzky, MD

Patient Health Questionnaire and Suicide Ideation

SOURCE: Simon GE, Coleman KJ, Rossom RC, et al. Risk of suicide attempt and suicide death following completion of the Patient Health Questionnaire depression module in community practice. *J Clin Psychiatry* 2016;77:221-227.

The most recent guidance from the U.S. Preventive Services Task Force endorses screening for depression in all adults. The Patient Health Questionnaire (PHQ) is a commonly used tool for depression screening. An attractive benefit about this screening tool is that no permission is required for copying and using the screener in clinical practice.

Simon et al reviewed results of PHQ screenings of more than 500,000 adults obtained during the 2007-2012 interval. Patients had visited primary care clinicians as well as mental health specialists. Among this population, there were 9,203 nonfatal suicide attempts and 484 suicide deaths recorded during the same interval.

Patients who reported "thoughts of death or self-harm" on the PHQ as "not at all" were seven-fold less likely to attempt suicide in the 2 years following their screening than those who responded with "nearly every day" (0.5% vs. 3.5% rate of suicide attempt). A similar relative risk of suicide death — five-fold increase in the latter group — was found.

Over time, incidence of suicide declined but remained elevated as much as two- to five-fold for at least 18 months post-positive screening. Hence, clinicians should take positive results on the PHQ seriously and institute appropriate suicide prevention methods. Unfortunately, no depression or suicide screener is perfect. More than one-third of all suicide attempts and deaths occurred within 30 days of responses by screenees who had answered "not at all" to the PHQ question, "In the past two weeks, have you had thoughts that you would be better off dead or of hurting yourself in some way?" ■

Pregabalin Improves Outcomes in Chronic Cough

SOURCE: Vertigan AE, Kapela SL, Ryan NM, et al. Pregabalin and speech pathology combination therapy for refractory chronic cough: A randomized controlled trial. *Chest* 2016;149:639-648.

Chronic cough without an evident etiology can be a challenging issue. Guidelines suggest etiologic considerations, including infectious, allergic, malignant, mechanical, and psychological issues. In the primary care setting, recommendations call for clinicians to consider a course of antihistamines/nasal steroids, inhaled short-acting beta-agonists, and proton pump inhibitors, respectively, to rule out occult allergic rhinitis/postnasal drip, cough-variant asthma, and gastroesophageal reflux disease. Speech pathology treatment (SPT) also has been shown to be effective in refractory cases. Unfortunately, even after such inclusive treatments, a not-insubstantial group of patients continues to have unexplained cough.

Vertigan et al performed a randomized, controlled trial of SPT combined with either pregabalin (up to 300 mg/d) or placebo in patients with refractory cough (n = 44). Treatment was administered for 14 weeks, and a follow-up visit one month post-treatment was performed to see if treatment effects persisted after discontinuation. Outcomes included cough frequency, severity, and quality of life, using recognized metrics.

Adding pregabalin to SPT improved cough severity and quality of life better than placebo. Encouragingly, improvements in outcomes were durable at the last visit, one month post-treatment. Pregabalin appears to provide meaningful improvement in cough for patients who have been refractory to other standard interventions. ■

A New Topical Treatment for Peyronie's Disease

SOURCE: Twidwell J, Levine L. Topical treatment for acute phase Peyronie's disease utilizing a new gel, H-100: A randomized, prospective, placebo-controlled pilot study. *Int J Impot Res* 2016;28:41-45.

Peyronie's disease is characterized by scarring of the tunica albuginea, which may result in angulation and/or pain when the penis is erect. While mild Peyronie's disease is largely inconsequential, unless the sufferer has cosmetic concerns about the appearance of the erect penis, moderate to severe Peyronie's disease may produce sufficient penile angulation as to make successful intercourse difficult or impossible.

Surgical intervention to modify the culprit scar lesion from the tunica is often successful, but many patients prefer less invasive interventions. Tools that have had some success with scar dissolution, such as intralesional verapamil, have not proven consistently effective in clinical trials.

H-100 oil is a combination of nicardipine and superoxide dismutase dissolved in emu oil, which is reportedly a good agent for enhancing transdermal absorption. Nicardipine blocks collagen production, and superoxide dismutase reduces inflammation through scavenging of free radicals.

Study subjects (n = 24) were randomized to H-100 or placebo. Both agents were applied twice daily to the penile shaft. At the six-month endpoint of the trial, men who applied H-100 demonstrated significant improvements in penile curvature and reductions in erection pain. Treatment was well tolerated, with only one patient discontinuing due to a penile rash. H-100 is a promising agent for a vexing disorder that otherwise often requires surgical intervention. ■

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CME QUESTIONS

1. **What percentage of outpatient oral antibiotic prescriptions in the United States in 2010-2011 may have been inappropriate?**

   a. 5

   b. 80

   c. 30

   d. 25

2. **The ILAE updated the definition of epilepsy in 2014 to allow for circumstances where a single unprovoked seizure could lead to a diagnosis of epilepsy where the risk of seizure recurrence is ___% or greater within the next 10 years.**

   a. 80

   b. 60

   c. 40

   d. 20

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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.

[IN FUTURE ISSUES]

Exposure to Greenness and Mortality in a Nationwide Prospective Cohort Study of Women

Daily Chocolate Consumption and Insulin Resistance and Liver Enzymes