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INSIDE

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Which Seasonal Flu Vaccine Is More Efficacious — The Shot or the Nasal Spray?

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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Dr. Gupta reports no financial relationship to this field of study.

Synopsis: *For the 2007-2008 season, the inactivated vaccine was more efficacious in preventing laboratory-confirmed symptomatic influenza A (predominately H3N2) in healthy adults than the live attenuated vaccine.*

Source: Monto AS, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009;361:1260-1267.

In the United States, the seasonal influenza epidemic is responsible for hospitalizing more than 200,000 Americans while killing more than 36,000 each year.[1] These numbers are sure to be much higher this season if we factor in the 2009 H1N1 influenza pandemic. While the Obama administration has declared it a national emergency, the vaccine against this type of novel influenza is slowly making its way to the various target groups in our nation. Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications. We can assume the same for the 2009 H1N1 influenza vaccine.

For the seasonal type, both the trivalent inactivated influenza vaccine (TIV) and the live attenuated influenza vaccine (LAIV) contain strains of influenza viruses that are antigenically equivalent to the annually recommended strains: one influenza A (H3N2) virus, one influenza A (H1N1) virus, and one influenza B virus. For the 2009 pandemic H1N1 type, both the monovalent inactivated

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vaccine (MIV) and the LAIV contain a single strain of the currently circulating 2009 pandemic influenza A (H1N1) virus. LAIV is administered intranasally by sprayer, whereas TIV or MIV is administered intramuscularly. LAIV is licensed for use among non-pregnant persons ages 2-49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications. TIV is licensed for use among persons ages ≥ 6 months, including those who are healthy and those with chronic medical conditions.

In the current study, Monto et al embarked upon the significant task of comparing the efficacies of the two types of seasonal influenza vaccine for the 2007-2008 flu season. It is essential to understand that the efficacy (i.e., prevention of illness among vaccinated persons in controlled trials) and effectiveness (i.e., prevention of illness in vaccinated populations) of influenza vaccines depend in part on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation (the match of the vaccine to the viruses actually circulating), and the outcome being measured. In the 2007-2008 season, type A (H3N2) viruses predominated; these viruses were characterized by a slight antigenic drift from the type A (H3N2) viral strain included in the vaccine. A total of 1952 healthy adults were enrolled in a randomized, double-blind, placebo-controlled, community-based study and received study vaccines in the fall of 2007. Absolute efficacy against both types of influenza was measured by isolating the virus in culture, identifying it on real-time polymerase chain reaction (PCR) assay, or both. A total of 119 participants (6.1%) developed laboratory-confirmed symptomatic influenza.

With the use of culture, real-time PCR, or both to confirm influenza cases, the absolute efficacy was 68% (95% confidence interval [CI], 46-81) for TIV and 36% (95% CI, 0-59) for LAIV. In terms of relative efficacy, there was a 50% reduction (95% CI, 20-69) in culture-confirmed or PCR-identified influenza among recipients of the inactivated vaccine as compared with those given the live attenuated vaccine. Since the majority of diagnosed cases were influenza A, the absolute vaccine efficacy in preventing laboratory-confirmed influenza A was 72% (95% CI, 49-84) for the inactivated vaccine but only 29% (95% CI, -14 to 55) for the live attenuated vaccine with a relative efficacy of 60% (95% CI, 33-77) for the inactivated vaccine.

■ COMMENTARY

When the vaccine and circulating viruses are antigenically well-matched, randomized controlled trials demonstrate that the effectiveness of TIV may be as high as 70%-90% in healthy adults ages < 65 years.[2] When the vaccine strains were antigenically dissimilar to the majority of circulating strains, the efficacy or effectiveness was significantly less (47%-77%) in studies.[2] Two similar studies in previous years by the same group of researchers have also demonstrated the vaccine efficacy for TIV to be higher, although the differences were statistically insignificant.[3,4] On the other hand, there are data to demonstrate that in young children, LAIV may be significantly more effective when compared to TIV.[5]

Whenever I observe inconsistent data, rather than drawing a firm conclusion, I often seek to understand where it may be leading us. While the statistics directly comparing the efficacy or effectiveness of these two types of vaccines may be insufficient at this time to identify whether one has a clear advantage over the other in large populations, it seems clear that LAIV may provide better protection in younger children and TIV better protection in adults.

Some scientists also theorize that the better efficacy of TIV in adults may be a consequence of previous exposure to seasonal influenza viruses over the years, resulting in some immunity to one or more strains of the live virus in LAIV, with ensuing rapid destruction of the live virus in the nasal mucosa by the individual's immune system. However, since the 2009 H1N1

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influenza virus is a novel type, the assumption is that the people taking the LAIV would be able to mount an immune response equivalent to the inactivated type of the vaccine. Therefore, most public health officials do not expect this kind of data to be replicated for the 2009 H1N1 vaccines. ■

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Chronic Bronchitis: Coughers and Spitters Die Young

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a retained consultant for Cephalon and Ventus, and serves on the speakers bureaus for Cephalon and Boehringer Ingelheim.

Synopsis: *People younger than age 50 who have cough and sputum production have increased all-cause mortality, risk of development of abnormal pulmonary function, and higher IL-8 and CRP levels, even if they have normal spirometry.*

Source: Guerra S, et al. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax* 2009;64:894-900.

THIS ANALYSIS COMES FROM THE TUCSON EPIDEMIOlogical Study of Airway Obstructive Disease (TESAOD). TESAOD is a population-based prospective cohort study that has been ongoing for more than three decades. At enrollment and every 2 years afterward, participants completed a standard respiratory questionnaire and underwent spirometry. The current report is based on those who, at the time of enrollment, were 21-80 years old, were not asthmatic, were not pregnant, had never had chest surgery, and had normal pulmonary function. Normal pulmonary function was defined as a forced expired volume in 1 second/forced vital capacity ratio (FEV1/FVC) of at least 70%. Chronic bronchitis was defined as cough and sputum production on most days for at least 3 months in at least 2 consecutive years. The investigators also recorded smoking history, performed skin prick tests, and measured serum immunoglobulin E (IgE), IL-8, CRP, and blood eosinophil counts at enrollment. Incident airflow limitation was defined as an FEV1/FVC ratio < 70% in any of the follow-up surveys. The vital status of TESAOD participants as of January 2005 was determined through direct contact with the family or designated next of kin of the participant, linkage with the Social Security Death Index, and linkage with the National Death Index.

Of the 1412 subjects eligible for analysis in this study, 97 (6.9%) reported chronic bronchitis (cough and sputum production on most days for at least 3 months in at least 2 consecutive years) at the time of entry into the study. As compared with subjects with no chronic bronchitis, those with chronic bronchitis at baseline were more likely to be males and smokers, had fewer years of formal education and slightly lower FEV1/FVC ratio at enrollment. There were no significant differences between the two groups in terms of age, body mass index, skin tests, total IgE levels, or eosinophilia.

With regard to mortality risk, 63% of the subjects who had chronic bronchitis at enrollment had died by 2005 as compared with 50% of the subjects with no chronic bronchitis ($P = 0.02$), despite the similar age distribution of the two groups at enrollment. The risk for all-cause mortality associated with chronic bronchitis was strongest among smokers and among subjects younger than 50 years of age.

During follow-up, 42% of subjects with chronic bronchitis at the beginning of the study developed airflow limitation (FEV1/FVC < 70%) vs 23% of those without chronic bronchitis ($P < 0.001$). Those with chronic bronchitis at baseline had a more than two-fold higher risk of developing airflow limitation if they were younger than 50 years of age, but the risk was not increased for those older than age 50.

The analysis of serum samples demonstrated that 66% of subjects with chronic bronchitis had elevated serum IL-8 vs 49% of subjects without chronic bronchitis at baseline. Similarly, serum CRP levels were higher among subjects with chronic bronchitis than in subjects with no chronic bronchitis, although this association was no longer significant after adjusting for covariates.

Not surprisingly, chronic bronchitis was strongly associated with cigarette smoking in this study, and its effects on incident airflow limitation, mortality risk, and systemic inflammation appeared stronger among smokers than never-smokers. In fact, there was no significant association between chronic bronchitis and any outcome in the never-smokers.

■ COMMENTARY

This is the first study to address by age the risk of death and disability posed by chronic bronchitis within the same population. The implication of this work is that those smokers who already have cough and sputum by the age of 50 have a markedly increased risk of death and declining pulmonary function. The authors speculate that the onset of symptoms is an early marker of susceptibility to the effects of cigarette smoking. This suggests that asking younger smokers about cough and sputum may allow identification and intervention in those at greatest risk.

The association between chronic cough and sputum is intriguing, and could represent a cost-effective screen for mortality. The biologic rationale for this finding may be that the airway inflammation in COPD may extend beyond the lung to systemic inflammation,[1-4] which has been implicated in the systemic manifestations and excess mortality of COPD. The authors hypothesize that early development of chronic bronchitis represents an early marker of susceptibility to both the proinflammatory effects and the long-term health consequences of cigarette smoking, which will affect the risk for incident COPD and mortality. ■

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Cardiac Resynchronization Therapy and Heart Failure

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *CRT combined with ICD decreased the risk of heart failure events in relatively asymptomatic patients with low ejection fractions and wide QRS complexes on their EKGs.*

Source: Moss AJ, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-1338.

Implantation of an automatic cardioverter-defibrillator (ICD) improves survival and reduces the risk of sudden death in appropriately selected patients with cardiac disease; however, ICD therapy is often associated with increased risk of first and recurrent heart failure events.[1-4] Cardiac resynchronization therapy (CRT) with biventricular pacing has been shown to be an effective adjunctive therapeutic addition to pharmacologic management in reducing the rate of hospitalization in symptomatic patients with advanced heart failure symptoms, an ejection fraction of 35% or less, and an intraventricular conduction delay of 120 msec or more.[5-7] Results from a previously published study suggested that CRT improves cardiac structure and function through reverse left ventricular remodeling.[8]

Moss and his colleagues designed a trial to determine whether CRT with biventricular pacing would reduce the risk of death or heart failure events in patients with mild cardiac symptoms, a reduced ejection fraction, and wide QRS complexes. They enrolled 1820 patients with ischemic or non-ischemic cardiomyopathy with an ejection fraction of 30% or less, a QRS duration of 130 msec or more, and New York Heart Association class I or II symptoms. Echocardiographic studies demonstrated substantial reductions in left ventricular end-diastolic and end-systolic volumes with improvement in the ejection fraction 1 year after the initiation of CRT-ICD therapy. They concluded that there was a 41% reduction in the risk of heart failure events, a significant reduction in left ventricular volumes, and improvement in the ejec-

tion fraction in patients treated with CRT; however, CRT did not reduce the overall risk of death.

■ COMMENTARY

Moss and his group demonstrated that the use of CRT combined with an ICD in asymptomatic or mildly symptomatic patients with heart disease, widened QRS complexes, and a reduced ejection fraction was associated with a 34% reduction in the risk of death or heart failure events as compared with patients who received ICD therapy alone. The observed benefit was driven by a highly significant 41% reduction in the risk of heart failure events, a finding that was evident primarily in the subgroup of patients with a QRS duration of 150 msec or more. CRT therapy was found to be associated with improvement in composite heart failure score during 12 months of follow-up in 419 patients with resynchronization turned on in the CRT devices as compared with 191 patients with resynchronization turned off in the CRT devices.[8]

In summary, CRT-ICD appears to significantly reduce the risk of heart failure events in vulnerable patients with ischemic or non-ischemic heart disease who have reduced ejection fractions and wide QRS complexes on their resting EKG, even if they have only minimal heart failure symptoms. ■

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Dietary Manipulation to Stabilize INR

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford serves on the speakers bureau for Pfizer.

This article originally appeared in the November issue of Clinical Cardiology Alert. *At that time it was peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco; Dr. Weiss reports no financial relationship to this field of study.*

Synopsis: A list of 16 vitamin K-rich foods can be used to develop a safe and feasible dietary management strategy in anticoagulated patients that may enhance achievement of target INR.

Source: de Assis MC, et al. Improved oral anticoagulation after a dietary vitamin K-guided strategy: A randomized controlled trial. *Circulation* 2009;120:1115-1122.

Erratic intraindividual INR values on chronic warfarin therapy are thought to be due to variability in vitamin K intake in the diet. Thus, de Assis et al from Brazil hypothesized that a dietary vitamin K management strategy would result in improved long-term anticoagulation as compared to traditional systems based upon drug-dose adjustments alone. In a single-center open trial, 132 patients requiring chronic anticoagulation with mechanical valves (58%) or atrial fibrillation (35%) were randomized to vitamin K-rich food intake

manipulation based upon INR or conventional INR-guided, drug-dosage adjustments. The primary endpoint was the percentage of patients within target INR range 90 days after randomization. Patients eligible for the study were those on therapy for > 3 months who had an INR value out of range but > 1.5 and < 4.0 and not experiencing bleeding or thrombosis.

One patient died, but not related to anticoagulation. The vitamin K group reached their target INR range more quickly than the conventional group and, at 90 days, 74% in the vitamin K group were at target compared to only 58% of the conventional group ($P = 0.04$). Minor bleeding was more common in the conventional group vs the vitamin K group (7 vs 1 patient; $P = 0.06$). de Assis et al concluded that a vitamin K dietary management strategy to achieve target INR in anticoagulated patients is feasible, safe, and may enhance achievement of target INR.

■ COMMENTARY

Maintenance of target INRs in patients over time is challenging. I have often told frustrated patients that if they ate the same thing every day we could keep them in perfect balance, but no one ever does that for obvious reasons. However, this study suggests that by paying attention to the intake of 16 foods, INR stability can be achieved. These foods are: arugula, asparagus, broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, cucumbers, green peas, green tea, lettuce, liver, spinach, turnip, vegetable oil, and watercress. They do not recommend avoiding these otherwise healthy foods, but keeping their intake constant. In the trial, they adjusted INR, if it was low, by cutting the intake of the vitamin K-rich foods by half. If the INR was high, they increased their intake by 100%. No restrictions on serving size were given, only directions to change the number of servings per week. Very few patients required parenteral vitamin K administration for over-anticoagulation (2 in the conventional group and 1 in the vitamin K group). Crossover to conventional management occurred in 11 patients in the vitamin K group (16%) because target INR could not be achieved with diet adjustments alone. Most of these patients never achieved target INR during the study period and, in 3, their INR was > 4.0.

The major limitation to this study is the short follow-up. We do not know if dietary adjustments will permit long-term stability without drug-dose changes. I suspect dosage adjustments and dietary control will be necessary long term, but if diet-control techniques minimize dosage changes and prolong the interval between blood samples, this would be a significant advantage. I am sure the nurses who often run anticoagulation clinics can learn how to assess diet and suggest adjustments; algorithms for this already exist. Whether long-term costs will be altered by this approach is not known. As a start, I am going to give my patients on warfarin a list of these 16 foods and tell them to keep the combined total number of servings of these foods the same each week and see if this helps stabilization. ■

Pharmacology Update

Benzyl Alcohol Lotion 5% (Ulesfia™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant 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 relationship to this field of study.

BENZYL ALCOHOL LOTION IS THE LATEST PRODUCT approved by the FDA for the treatment of head lice (*Pediculosis capitis*) infestation. Benzyl alcohol acts by inhibiting lice from closing their respiratory spiracles. This allows the vehicle, mineral oil, to facilitate obstruction of their airways and, ultimately, asphyxiation of the lice.[1] The 5% lotion is marketed by Sciele Pharma as Ulesfia™.

Indications

Benzyl alcohol lotion is indicated for the topical treatment of head lice infestation in patients 6 months of age and older.[1]

Dosage

The lotion should be applied to dry hair and the dose is based on the length of the hair, varying from 4 to 6 oz for short hair (0-2 inches) up to 32-48 oz (> 33 inches).[1] After 10 minutes the lotion should be rinsed off with water. Application should be repeated in 7 days. After the lotion has been washed off, a fine-tooth comb should be used to remove treated lice and nits from the hair and scalp. Use of the product in patients younger than 6 months of age is not recommended because of potential for increased systemic absorption due to high body surface to body mass ratio and immature skin barrier.[1]

Benzyl alcohol is available as a 5% lotion in 8 oz bottles.

Potential Advantages

Based on its mechanism of action, i.e., suffocating the lice, resistance to benzyl alcohol is unlikely to develop.

Potential Disadvantages

Benzyl alcohol is moderately effective (75% lice-free for 14 days) and is not an ovicide.[1,2] Most common adverse events are pruritus (12%), erythema (10%), pyoderma (7%), and ocular irritation (6%).[1]

Comments

Benzyl alcohol is the latest product approved for the treatment of head lice. Efficacy was demonstrated in two multicenter, randomized, double-blind, vehicle-controlled studies in 250 subjects (6 months of age and older) with active head lice.[1] Treatment involved 2 applications separated by 1 week. The proportions of subjects free of live lice 14 days after the last treatment were 76.2% for benzyl alcohol vs 4.8% for the vehicle in study 1 and 75% and 26.2%, respectively, for study 2.

Clinical Implications

Head lice are a common infestation in the United States among children 3-12 years of age. Approximately 6-12 million are infested annually.[2] Permethrin 1% Crème rinse is currently the recommended treatment by the American Academy of Pediatrics. However, resistance to permethrin has been reported.[3] In two recent studies, permethrin showed cure rates of 67.6% in one and 62-68% in the other.[4,5] Malathion lotion is highly effective (98%) and is ovicidal but has an odor, a prolonged application time (8-12 hours), and is flammable.[6] Benzyl alcohol lotion showed a cure rate of about 75% but is not an ovicide. It does provide another treatment option that appears to be similar to or marginally better than permethrin. ■

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CME Questions

59. Which of the following variables least describes the factors upon which the efficacy and effectiveness of influenza vaccines depend?

a. The age of the vaccine recipient
b. The gender of the vaccine recipient
c. The immune status of the vaccine recipient
d. The degree of similarity between the viruses in the vaccine and the disease in the community

60. Symptoms of cough and sputum in smokers with normal spirometry are associated with increased mortality only in:

a. women.
b. men.
c. those older than 50 years of age.
d. those younger than 50 years of age.

61. Cardiac resynchronization therapy combined with ICD:

a. decreased the risk of heart failure events in symptomatic patients only.
b. decreased the risk of heart failure events in patients with ischemic cardiomyopathy but not in those with non-ischemic cardiomyopathy.
c. should be used in all heart failure patients.
d. significantly reduced the risk of heart failure events in relatively asymptomatic patients with low ejection fractions and wide QRS complexes on EKG.

Answers: 59. b, 60. d, 61. d.

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Sucampo Pharmaceuticals, Takeda, Boehringer Ingelheim; and is a consultant and on the speaker's bureau for Novo Nordisk, Lilly, Daiichi Sankyo, Forest Pharmaceuticals, Cephalon, Novartis, and Sanofi Aventis.

Surgery vs Medical Treatment for CTS

Source: Jarvik JG, et al. *Lancet* 2009; 374:1074-1081.

Several trials comparing surgical with medical therapy for carpal tunnel syndrome (CTS) have been insufficient to clarify the optimum approach. Similarly, it is largely unknown which CTS characteristics predict a favorable response to either type of treatment. Jarvik et al conducted a controlled trial of CTS patients (n = 116) randomized to medical or surgical treatment. Additionally, wrist MRI and nerve conduction studies were performed to identify the predictive capacity of these metrics.

Surgical intervention consisted of either open or endoscopic carpal tunnel decompression (per surgeon preference). Medical treatment included ibuprofen 200 mg tid, physical therapy provided by a hand therapist, other analgesics, corticosteroid injections, and ultrasound (all as per clinician preference). The primary outcome was function as measured by the Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) at 12 months.

There were no serious adverse events in either treatment group. At 12 months, although both groups showed substantial improvement, the CTSAQ score was significantly better in the surgical group. Study subjects with baseline nerve conduction deficits responded less well to surgical intervention. On MRI, patients with signs of nerve edema (indicative of more advanced disease severity) had successful outcomes (30% improvement on the CTSAQ) only half as often as those without edema. In patients with more severe baseline disease, difference in outcome between surgery and medical management diminished. Overall, surgical intervention provides outcomes that are superior to medical therapy. MRI and nerve conduction data may assist patient selection. ■

Does Metformin Affect Thyroid Function?

Source: Cappelli C, et al. *Diabetes Care* 2009;32:1589-1590.

Diabetes commonly is comorbid with other endocrinopathies, including hypothyroidism and hypogonadism. The most common first-line pharmacotherapy for diabetes is metformin, which has been heretofore considered an essentially benign drug, when proscriptions for its use (e.g., renal insufficiency, heart failure) are observed. Recent reports have suggested that metformin might have an effect on TSH even when levothyroxine replacement doses are kept constant; since many hypothyroid patients are diabetic, such effects may be worthy of note.

Capelli et al evaluated in a pilot study 11 diabetic patients with hypothyroidism who initiated therapy with metformin. All had been on stable doses of levothyroxine. Thyroid studies (TSH, free T4 and T3, and total T4 and T3) were performed at baseline, 6 hours, 24 hours, 72 hours, and 3 and 6 months after initiation of metformin. They included in their analysis additional data from another study population comprised of diabetics receiving thyroid for various indications, diabetics with subclinical hypothyroidism not receiving levothyroxine replacement, and diabetics with normal thyroid function.

During the pilot study, despite continued stable levels of levothyroxine replacement and other thyroid parameters, the mean TSH dropped from 2.11 to 1.5 mIU/L. Omission of metformin in one patient who had experienced a more dramatic TSH decline resulted in a return of TSH to baseline. Particularly in the diabetic group with subclinical (non-replaced) hypothyroidism, the decline in TSH was apparent: from a mean of 4.5 to 2.93 mIU/L at 1 year. The mechanism by which metformin lowers TSH is not known. ■

Beleaguered Primary Care Clinicians

Source: Krasner MS, et al. *JAMA* 2009;302:1284-1293.

If data obtained within the last 5 years are correct, the majority of primary care physicians (PCPs) report emotional exhaustion, depersonalization, and/or low sense of accomplishment — collectively called burnout. The favorable results of an intervention to alleviate burnout deserve our focus.

Primary care physicians (n = 70) in Rochester, NY, participated in a year-long intervention: 8 weeks of intensive intervention, followed by once-monthly maintenance for 10 months. Although the complexity of intervention was too great to be captured in this communication, didactic materials (including presentations on dealing with conflict, reflecting on meaningful experiences, etc.), meditation (including yoga-type exercises), and narrative exercises (for instance, writing and sharing brief stories about challenging experiences in practice) were included. Sessions occupied 2.5 hours/week for 8 weeks, followed by monthly maintenance 2.5-hour sessions for 10 months. A single all-day session of mindfulness meditation was included during week 6-7.

Following the intervention, scores on the Maslach Burnout Inventory showed meaningful improvements. Although this is a time-intensive investment, it is encouraging to see tools through which clinicians might better enjoy, be better fulfilled by, and probably perform more effectively in their practice. ■