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# Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

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ABSTRACT & COMMENTARY

# You Are What You Feed Your Gut Microbiome

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

SYNOPSIS: The human gut microbiome regulates intestinal function and health. There is mounting evidence that the gut microbiome influences the immune system and the central and peripheral nervous systems. This article reviews the bidirectional relationship between the gut microbiome and brain disorders.

SOURCE: Petra AI, et al. Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune dysfunction. *Clin Ther* 2015;37:984-995.

These authors reviewed articles on Medline starting in 1980 for a wide range of neurologic disorders and two systems, the gut-microbiota-brain axis and the hypothalamic-pituitary-adrenal axis. Bidirectional influences exist between the brain and the gut flora that are associated with mood disorders, autism spectrum disorders, attention deficit hypersensitivity disorder, multiple sclerosis, and obesity. This article joins a growing list of other studies illuminating these relationships.[1-4]

Bacterial dysbiosis, small intestinal bacterial overgrowth, and increased intestinal permeability may produce numerous immunologic effects, including central nervous system (CNS) inflammation. Our mood is affected by these changes. Bacterial proteins cross-react with human antigens to stimulate dysfunctional responses of the immune system that may lead to neurodegenerative disorders.

Communication between the gut and the brain goes both ways. Antibiotics, environmental

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Internal Medicine
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and infectious agents, intestinal neurotransmitters, sensory vagal fibers, cytokines, and essential metabolites all convey information to the CNS about the intestinal state. The hypothalamic-pituitary-adrenal axis is the CNS regulatory area of satiety, and neuropeptides released from sensory nerve fibers affect the gut microbiota composition directly or through nutrient availability. Such interactions appear to influence the pathogenesis of a number of nervous system disorders, from mood disorders to autoimmune and neurodegenerative conditions to obesity.

## ■ COMMENTARY

"You are what you eat" is an age old expression highlighting that we are organisms that depend on food for growth and survival. The title even became a popular diet and TV program in the United Kingdom from 2004-2007. With the emphasis in modern medicine on pharmacologic therapies and procedures, the vital importance of nutrition has been downplayed in human health and disease. Many people eat whatever they want, and healthcare does little to intervene. We continue to have debates on what constitutes a healthy diet.

The recent appreciation of the gut microbiome, the 100 trillion organisms that reside within us, has added a new dimension to this expression. These gut bacteria together weigh about 10 pounds and would occupy a half gallon container. They are a new vital organ to the human species. They completely depend on us for sustenance.

The gut microbiome is an important intermediary between what we eat and our health. The gut bacteria get first crack at what we eat and play a vital role in what gets into our bodies and what happens to these nutrients. A healthy gut microbiome is critical for good health, and an unhealthy gut microbiome assures that we will not be well.

The science around the gut microbiome is in its infancy. The Human Microbiome Project at the NIH was established in 2008.[5] The emerging knowledge from this "new organ" is a paradigm shift for medicine. Hopefully, it will usher in renewed interest in human nutrition and its impact on our health. ■

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## ABSTRACT & COMMENTARY

# Prostate Cancer and Smoking: One More Reason to Trash the Tobacco

***By Martin S. Lipsky, MD***

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**Dr. Lipsky is a retained consultant for Health Solutions & Strategies.**

SYNOPSIS: While smoking is associated with a wide range of cancers, the link between prostate cancer and smoking is tenuous. This study showed that following prostatectomy for cancer, smokers and ex-smokers had a higher risk of recurrence.

SOURCE: Rieken M, et al. Association of cigarette smoking and smoking cessation with biochemical recurrence of prostate cancer in patients treated with radical prostatectomy. *Eur Urol* 2015 Jun 3. pii: S0302-2838(15)00440-6. doi: 10.1016/j.eururo.2015.05.038 [Epub ahead of print].

Smoking is a well-known risk factor for many types of cancer. However, evidence establishing a link between smoking and the incidence of prostate cancer is tenuous and often contradictory.[1] While the association between smoking and the incidence of prostate cancer remains unclear, cigarette smoking does seem to be a dose-dependent risk factor for prostate cancer mortality.[1]

In this multi-institution study, Rieken et al investigated the association between smoking status, time since smoking cessation and cumulative smoking, and the risk of biochemical recurrence of prostate cancer in patients treated with radical prostatectomy for prostate cancer.[2]

Using six centers, the cohort included 7426 patients with prostate cancer treated with radical prostatectomy from 2000 to 2011. Patients with incomplete data and those with positive lymph node metastases were excluded from the study, leaving 6538 patients available for analysis. Follow-up was performed according to institutional protocols, but generally patients were seen quarterly in the first year, semiannually in year two, and then annually. The primary endpoint was defined as a PSA > 0.2 ng/mL on two consecutive tests. The day an elevation was first detected was defined as the day of a recurrence. If patients died during the study, they were only considered as recurrent if the PSA was elevated before death. No patients received radiation, hormonal, or chemotherapy.

The mean duration for patients not experiencing a biochemical recurrence was 28 months (range 14-42 months). Smoking status was significantly associated with biochemical recurrence (BCR)-free survival, with BCR-free survival rates of 90%, 84%, and 83% in never, former, and current smokers, respectively. A significant association between smoking and a higher risk of recurrence was observed for all Gleason scores. No significant association with cumulative smoking and recurrence was found. Smoking cessation was associated with a reduced risk of recurrence.

The authors concluded that smoking status was associated with a higher risk of recurrence, with former and current smokers experiencing almost a two-fold increase in risk. The duration of time since an individual stopped smoking also was associated with recurrence risk. Those who stopped smoking < 10 years ago experienced an increased risk while those > 10 years was similar to nonsmokers.

## ■ COMMENTARY

This study provides yet another reason not to smoke. While it is not clear how and to what amount smoking contributes to an increased incidence of prostate cancer, smoking increases the risk of dying from prostate cancer. Smokers should be counseled regarding the connection of prostate cancer mortality and smoking. In primary care, physicians need to take advantage of "teachable moments," when patients are most likely to listen and act on lifestyle advice. For cardiovascular disease, hospitalization for a cardiovascular event provides that moment when patients are more motivated to adjust to a healthier lifestyle. In addition to routinely counseling about tobacco use, perhaps undergoing a prostate biopsy or cystoscopy to rule out bladder cancer provides another teachable moment in the battle against tobacco use. ■

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ABSTRACT & COMMENTARY

# Statin Use and Cognitive Effects: Not a Brain Drain


***By Susan T. Marcolina, MD, FACP***

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


SYNOPSIS: Despite earlier concerns by the FDA about adverse effects of statins on cognitive functioning, a meta-analysis of data from more than 28,000 patients enrolled in 18 randomized, placebo-controlled trials of statin therapy failed to show a causal relationship

between treatment and adverse neurocognitive effects for patients with and without cognitive impairment.

SOURCE: Ott BR, et al. Do statins impair cognition? A systemic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015;30:348-358.

A consumer advisory issued by the FDA in February 2012 regarding potential adverse effects of statins on cognitive functioning concerned both physicians and patients, given the widespread use of statins for primary and secondary prevention of atherosclerotic cardiovascular disease, and hyperlipidemia treatment.[1] The postmarketing adverse reports, reported via the Adverse Event Reporting System, upon which the FDA based its warnings, generally described individuals older than 50 years age who experienced ill-defined memory loss, confusion, and foggy thinking with variable onset of symptoms ranging from 1 day to years after statin exposure. The statins involved were primarily the lipophilic statins simvastatin and atorvastatin. These symptoms resolved after discontinuation of the statins and in some instances recurred with resumption.

Ott and colleagues' meta-analysis and systematic review is timely and comprehensive in scope in its purpose to synthesize current evidence linking statin use with adverse cognitive outcomes. Since the public health implications of the FDA advisory were enormous, the authors compiled information on statin therapy and neurocognitive testing outcomes from all of the major randomized, placebo-controlled trials (RCTs) of statin therapy from several sources including Cochrane Central trial registries, MEDLINE, and EMBASE. Outcomes were analyzed separately in studies of both cognitively normal participants and in cognitively impaired trial patients with a diagnosis of Alzheimer's disease, and were designed to detect signals for adverse neurocognitive outcomes utilizing a summary statistic called the standardized mean difference (SMD).

SMDs are used in meta-analyses when the same outcome is being measured (neurocognitive outcomes in this case) using different psychometric scales. SMD values of ± 0.2 imply small differences, particularly when confidence intervals (CI) are narrow.[2]

For the 14 RCTs of cognitively normal patients included in the quantitative analysis, nine of the trials enrolled healthy patients without a specified medical diagnosis (age range 18 to 70 years), and five enrolled patients with cardiovascular risk factors (age range 40 to 83 years). Cognitive test outcomes among these participants at baseline included both global functioning and specific domains such as attention, executive function, memory, processing speed, and working memory.

For the four RCTs of cognitively impaired patients with Alzheimer's disease (mean age > 68 years), cognitive test outcomes were assessed with either the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) or the Mini-Mental Status Examination. The ADAS-Cog measures language and memory and can determine incremental improvements or declines in cognitive functioning, which are important metrics in this group of patients.

This meta-analysis of the cognitive test data collected from these trials failed to show significant adverse effects of statins across all the measured cognitive domains in cognitively intact trial participants (SMD 0.01; 95% CI, -0.01 to 0.03; $P = 0.42$) or Alzheimer's disease trial participants (SMD -0.05; 95% CI -0.19 to 0.10, $P = 0.38$).

The authors also noted that adverse cognitive outcomes attributable to statins were rarely reported in trials involving cognitively normal or impaired subjects.

## ■ COMMENTARY

The time has now come to breathe a sigh of relief and reassure patients who require statin therapy that these medicines will not cause cognitive impairment.

This is an important message of reassurance because statins (HMG CoA reductase inhibitors) are the drugs of first choice for risk modification in patients at high risk for cardiovascular and cerebrovascular disease, the leading causes of death and disability (including cognitive disability) among adult patients. As a matter of fact, high levels of adherence and longer duration of statin therapy are associated with progressively increasing clinical benefits in terms of primary and secondary prevention of cardiovascular events.[3] The statin-associated relative risk reductions of 20-30% for myocardial infarction, 20% for ischemic stroke, and 10-15% for all-cause mortality underscore the importance of these medications.[4]

The multiple mechanisms of action by which statins mitigate risk include: 1) decreases in LDL cholesterol, 2) modification of inflammatory response, 3) antioxidant effects, 4) antithrombotic effects, and 5) plaque stabilization effects such as reduction of smooth muscle proliferation and cholesterol accumulation.[5,6]

In 2013, a meta-analysis of eight randomized, controlled, statin-treatment trials showed no evidence of altered cognitive function between statin-treated

and control patients.[7] A systematic review of three RCTs and 24 observational studies published in the same year showed that statin treatment was not associated with increased risk for incident dementia, Alzheimer's disease, or mild cognitive impairment. During the course of the study, Richardson et al reviewed the FDA postmarketing surveillance databases and found that the reporting rates for cognitive adverse events were similar for statins, losartan, and clopidogrel, although no studies suggested memory losses from the latter two commonly prescribed medications.[8]

Another important factor to consider about the FDA advisory was that the Adverse Event Reporting System reports that formed the basis of the warning did not mention concomitant medications taken by patients at the time of the adverse cognitive events. Several types of medications may impair statin disposition and metabolism, especially for high-intensity therapy and for statins primarily metabolized by the P-450 cytochrome enzyme system. Simvastatin, in particular, as a cytochrome P-450 3A4 inhibitor, when taken in conjunction with macrolide antibiotics (3A4 inhibitors) or amiodarone (3A4 substrate and inhibitor), can result in both increased risk for QT prolongation and arrhythmias and statin-induced myopathy.

Although clinician and patient concerns about statins causing cognitive decline can largely be allayed as a result of this study, new onset of cognitive decline in a patient on statins for cardiovascular risk reduction deserves evaluation. It may be reasonable to discontinue certain other medications and screen for dementia, depression, as well as endocrine, infectious, inflammatory, vascular, and other degenerative illnesses, as root causes. It may be also reasonable to give a statin holiday. This presents an opportunity for a patient-centered discussion of options. ■

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PHARMACOLOGY UPDATE

# Eluxadoline Tablets (Viberzi) and Rifaximin (Xifaxan) Tablets


***By William T. 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 two new treatments for irritable bowel syndrome with diarrhea (IBS-D). Eluxadoline is a new chemical entity that is a mu-opioid receptor agonist and a delta-opioid receptor antagonist, which causes reductions in gastrointestinal contraction. The second treatment is a new indication for rifaximin, an antibiotic previously approved for the treatment of traveler's diarrhea and recurring hepatic encephalopathy.

Eluxadoline is marketed by Patheon Pharmaceuticals and marketed as Viberzi. The brand name for rifaximin is Xifaxan.

## INDICATIONS

Both drugs are approved for treatment of IBS-D.

## DOSAGE

Eluxadoline: 100 mg twice daily taken with food.[1]

The dose should be reduced to 75 mg twice daily with food in patients without a gallbladder, unable to tolerate the 100 mg dose, with mild or moderate hepatic impairment, or taking concomitantly OATP1B1 inhibitors (e.g., antiretroviral protease inhibitors, cyclosporine, rifampin, or gemfibrozil).

Rifaximin: 550 mg three times a day for 14 days.[2] Treatment may be repeated twice if recurrence occurs.

## POTENTIAL ADVANTAGES

Eluxadoline and rifaximin provide new treatments with different mechanisms of action. Rifaximin offers a 14-day treatment course, compared to chronic administration for eluxadoline.

## POTENTIAL DISADVANTAGES

Eluxadoline is contraindicated in patients with known or suspected biliary duct obstruction, dysfunction of the sphincter of Oddi, alcoholism, history of pancreatitis, severe hepatic impairment, or severe constipation. The drug has the potential to increase the spasm of the sphincter of Oddi.[1] The effect of antibiotic resistance of GI flora with long-term and wide-spread use of rifaximin is not known.[5]

## COMMENTS

Irritable bowel syndrome (IBS) is a common, difficult-to-treat, functional GI disorder characterized by recurrent symptoms.[5] There are no well-linked measurable physiological abnormalities or measurable biologic markers. Patient-reported outcomes are the only way to assess treatment efficacy.[3] The FDA guidance for IBS recommends studies enroll subjects who meet the specified Rome III IBS diagnostic criteria.[3] These include a weekly average of worst daily (in the past 24 hours) abdominal pain score of ≥ 3.0 on a 0 to 10 point scale, as well as stool consistency, which is defined as at least one stool with a consistency of type 6 (mushy or fluffy) or type 7 (watery) Bristol stool score (BSS) on at least 2 days per week or an average daily BSS score of ≥ 5.5 and at least 5 days with a BSS score ≥ 5 over the week before randomization.

Response is defined as ≥ 30% improvement from baseline in the weekly average abdominal pain in the past 24 hours score and at least a 50% reduction in the number of days in a week with a daily stool consistency of BSS type 6 or 7 compared to baseline, or a reduction in the BSS to < 5 on at least 50% of the days within a 12-week time interval.

Eluxadoline was evaluated in two 26-week randomized, double-blind, placebo-controlled trials (n = 2426). Subjects were randomized to 100 mg or 75 mg twice daily, or they were given a placebo. The response rates over 26 weeks for the two studies were 23% and 30% for 75 mg, 29% and 33% for 100 mg, and 19% and 20% for placebo.[1] Treatment differences were 4% and 10% for the lower dose and 10% and 13% for the 100 mg dose. The results were statistically different than placebo for the 100 mg dose in both studies and for the 75 mg dose in one study. Eluxadoline appears to have greater benefit in improving stool consistency than abdominal pain.

Rifaximin was evaluated in three randomized, double-blind, placebo-controlled trials, with two studies meeting Rome II criteria and one that included subjects who met Rome III criteria (n = 2579).[2,4] Subjects were randomized to 550 mg three times daily or placebo for 14 days, and treatment success was evaluated at the end of a 4-week follow-up period. Responders were followed for recurrence. The response rate during weeks 3 to 6 was 38% for rifaximin and 31% for placebo, with a treatment difference of 7% (95% confidence interval, 0.9-16.9). Fifty-nine percent of responders had a recurrence with a median time of 10 weeks (range 6 to 24 weeks).

Common side effects for eluxadoline include nausea, constipation, and abdominal pain in the range of 6-8%. Common side effects for rifaximin were similar to placebo.[4]

## CLINICAL IMPLICATIONS

Both drugs appear to provide modest benefit in IBD-D. The absolute percent differences were 10-13% for eluxadoline and 7% for rifaximin, with a 59% recurrence. Response rates were modest compared to placebo. There are no direct comparisons between the two drugs. Alosetron is the only other currently FDA-approved treatment for IBS. However, the drug carries a boxed warning for serious complications of constipation and acute ischemic colitis and is only approved for females. As of 2014, the American College of Gastroenterology does not have a highly effective treatment for IBS-D when considering a wide variety of treatments from diet, probiotics, antispasmodics, antidepressants, rifaximin, alosetron, etc.[5] Rifaximin is currently available at a wholesale cost of $1177 per treatment course. Eluxadoline is a opioid and is expected to be a schedule drug. Its expected availability is early 2016. ■

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*Continued on page 128*

# Clinical Briefs

By Louis Kuritzky, MD

## Oral Nutritional Supplementation for Hospitalized COPD Patients Pays Off

SOURCE: Snider JT, et al. Effect of hospital use of oral nutritional supplementation on length of stay, hospital cost, and 30-day readmissions among Medicare patients with COPD. *Chest* 2015;147:1477-1484.

In contrast to many of the other top 10 causes of death in the United States, chronic obstructive pulmonary disease (COPD) deaths are increasing, such that COPD is now the third most common cause of death. Although a variety of pharmacologic interventions are available to improve symptoms and decrease exacerbations, none has been shown to reduce mortality.

COPD is associated with increased risk for malnutrition, which may lead to further respiratory function compromise and immune dysfunction. Might nutritional supplementation of patients admitted for COPD improve outcomes?

Snider et al utilized the Premier Research Database, which contains hospitalization information from 460 U.S. hospitals and 46 million hospitalizations. The authors compared outcomes in persons > 65 years of age admitted for COPD (n = 378,419) who received oral nutritional supplementation (n = 10,322) vs those who did not. Outcomes of interest were length of hospital stay, hospitalization costs, and readmission rates.

Oral nutritional supplementation was associated with numerous favorable results: Length of stay was reduced by 21.5%, readmission rate was reduced by 7%, and even the cost of hospitalization was reduced by 12.5%. Overall, the results suggested that for every dollar spent on oral nutritional supplementation, the hospital saved $18.

It is clear oral nutritional supplementation has been employed in a small minority of COPD admissions (10,322 out of 378,419 admissions). These favorable results should prompt reconsideration of the value — health wise and economic — of oral nutritional supplementation in patients admitted for COPD. ■

## An Unrecognized Relationship Between Asthma and Obesity

SOURCE: Pakhale S, et al. Effects of weight loss on airway responsiveness in obese adults with asthma: Does weight loss lead to reversibility of asthma? *Chest* 2015;147:1582-1590.

The prevalence of asthma is increasing, although the reasons behind this are not entirely clear. There may be an important link between asthma and obesity.

For instance, incident asthma is almost 50% more common in obese persons. Each increment of three units in body mass index (BMI) is associated with a 35% increase in asthma. Even the degree of airway hyperreactivity — the hallmark of asthma — is directly related: For each one-unit increase in BMI (e.g., a BMI change from 30 to 31 kg/m$^2$), there is a 3% increase in airway hyperreactivity.

Whether treatment of obesity might benefit patients with asthma has received little attention in the literature. Pakhale et al performed a prospective controlled trial in obese adults (mean BMI = 45 kg/m$^2$) with asthma to compare metrics of pulmonary function and airway hyperreactivity in subjects who participated in a weight loss program vs control. The intervention group received lifestyle intervention to enhance dietary weight loss and exercise.

The metric for airway hyperreactivity was the PC20 — the amount of methacholine necessary to produce a bronchoconstrictive effect large enough to reduce $FEV_1$ by 20% (the more methacholine it takes, the less hyperreactive your airways are).

At the end of the 3-month trial, the intervention group had lost a mean of approximately 17 kg, but the control group had a gain of approximately 1 kg. The intervention group enjoyed improvements in pulmonary function (improved $FEV_1$), asthma quality of life, and PC20. Weight reduction may be an overlooked tool for asthma management. ■

## Sound Stimulation in Alzheimer's Patients

SOURCE: Clements-Cortes A, Bartel L. Sound stimulation in patients with Alzheimer's disease. *Annals Long-Term Care* 2015;23:10-16.

Music therapy can be a helpful and pleasurable experience for patients with Alzheimer's disease (AD). Although clinical trials on the subject are not large or plentiful, the favorable results obtained appear promising. For instance, one clinical trial looked at the impact of music therapy among persons with agitation and AD. A 45-minute session of music therapy reduced agitated and disruptive behaviors (like swearing or yelling). Whether music therapy provides long-term benefits has not been well studied.

For most, if not all of us, music has deep-rooted emotional links. Background music has been shown to improve cognitive performance throughout the adult lifespan, including college students, older adults, and patients with AD. Interestingly, those brain areas responsible for processing music are commonly preserved in patients with AD, despite their loss of other cognitive functions. At a less macroscopic level, exposure to music has been shown to increase levels of IgA and decrease cortisol.

Whether clinicians want to consider supporting the use of recreational environmental music (simple background music for patients) or the formal structure of music therapy provided by a trained therapist, music may provide meaningful clinical improvements in AD patients, as well as an enhanced quality of life. ■

*Continued from page 126*

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## CME QUESTIONS

**1. Which statement about the gut microbiome and the brain is true?**

a. The gut microbiome is largely independent of our diet and its main role is to help in digestion.

b. The vagus nerve is a critical pathway for interactions between the gut microbiome and the nervous system.

c. The communication between the gut microbiome and the brain are in one direction from the gut to the brain.

d. Antibiotics are important to improve the health of the gut microbiome.

**2. Which of the following statements is not true?**

a. Smoking doubles the incidence of prostate cancer.

b. Smoking doubles the risk of prostate cancer recurrence.

c. The risk of prostate cancer recurrence in those who have not smoked for at least ten years is similar to nonsmokers.

d. It is never too late to stop smoking.

**3. Statin drug use modifies risk for cardiovascular and cerebrovascular disease.**

a. True

b. False

## 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.

## [IN FUTURE ISSUES]

Cryptogenic stroke and atrial fibrillation

Antibiotics for acute appendicitis