

# the SECOND OPINION

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A monthly medical newsletter for the Athens medical community

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## SMOKING GUN (CONT.)

6. Decide on a "workable action plan" for immediate intervention when cravings occur, including phone counseling, peer support, nicotine augmentation;
7. Serially monitor blood cotinine levels.

## ANA TEST

The anti-nuclear antibody (ANA) test is a useful screen for vasculitic conditions, autoimmune conditions with protean clinical manifestations, which are clinically suspected in multi-systemic disorders in IV drug abusers or smokers, or those presenting with palpable purpura, fever of unknown origin, idiopathic thrombocytopenia, unexplained skin lesions, cardiac murmurs, recurrent obstetric attrition/fetal wastage or thrombo-embolic disease. Differential considerations (besides vasculitis) include cholesterol emboli, cardiac myxoma, anti-phospholipid antibody syndrome, (sub-acute) bacterial endocarditis, sepsis and Bueger's disease.

A positive ANA test may precede the clinical presentation of vasculitis. Positive titers are common in healthy individuals, especially with advanced age, and more commonly in females. Therefore, the ANA test is sensitive but not specific: a titer of >1:40 is found in 30% of the normal population, >1:80 in 12% of the population, >1:160 in 5%, and >1:320 in 3% of the population. ANA is always positive in 3 conditions, and are therefore integral to making those diagnoses: drug-induced lupus (typically triggered by procainamide, penicillamine, isoniazid, hydralazine, oral estrogens, phenytoin), autoimmune hepatitis and mixed connective tissue disease. ANA is positive in 95% of systemic lupus erythematosus (SLE) patients, 95% of mixed connective tissue disease, 75% of scleroderma, 70% of juvenile chronic arthritis, 50% of Sjogren's disease, 40% of rheumatoid arthritis and 33% of all elderly Caucasians. ANA positivity (at widely variable titers) is also found in chronic infections (such as bacterial endocarditis and tuberculosis), viremia (especially hepatitis C, HIV and infectious mononucleosis), lympho-proliferative disease, primary pulmonary hypertension, Raynaud's syndrome, and a host of autoimmune disorders such as dermatomyositis, type 1 diabetes mellitus, primary biliary cirrhosis, Addison's disease, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia and Hashimoto's thyroiditis.

**To help add specificity to a positive ANA screen, several strategies have been used:**

1. Nuclear staining pattern (in reality, this test is neither sensitive nor specific, as different disease states can give the same staining pattern; generally, a diffuse/homogeneous staining pattern is consistent with SLE and mixed connective tissue disease; a speckled pattern is consistent with scleroderma, polymyositis, mixed connective tissue disease, rheumatoid arthritis and Sjogren's disease; a nucleolar pattern is consistent with scleroderma and polymyositis; a peripheral/rim pattern is consistent with SLE; a centromere pattern is consistent with scleroderma).
2. Specific auto-antibody tests (anti-double stranded DNA antibody is positive in 50% of SLE, but also weakly positive in IV heroin use; anti-ribonucleoprotein U1 RNP is found in mixed connective tissue disease, but uncommonly in localized scleroderma; anti-Smith antibody found only in [25% of cases of] SLE; anti-histone H1/H2 antibodies in SLE; anti-histone H3/H4 in drug-induced lupus; anti-Jo 1 tRNA synthetase antibody in 25% of polymyositis; anti-scl 70 in 50-70% of systemic sclerosis; anti-centromere antibody in 90% of CREST syndrome; anti-SS A [Ro]/anti-SS B [La] antibody in scleroderma)

**Take Home Message:** the positive predictive value of an ANA titer >1: 1080 is ~100% for SLE/vasculitis, and the negative predictive value that a titer <1:80 is not SLE is ~100%.

## A BIG FAT LIVER

In considering drug treatment for non-alcoholic steato-hepatitis, note that:

1. Orlistat can help with accelerated weight loss
2. Metformin augments weight loss but does not necessarily improve liver histology
3. Thiazolidinediones (Actos, Avandia) improve liver histology but may actually increase weight gain
4. Statins (Lipitor, Crestor) are effective but should be serially monitored for secondary transaminitis (biochemical "relapse")
5. Pentoxifylline does not have consistent effects in several clinical trials

## FROM THE EDITOR

It has been one of those weeks. I was completing service call, and between chowing down on fried chicken (courtesy of your friendly neighborhood cardiologist, thank you) and treating dialysis-induced pseudo-seizures in the Emergency Room (I kid you not), I had the dubious pleasure of watching televised portions of the health care summit. Call it epiphany or just being naive, but it soon dawned on me that each party was reading from a totally different script. On one side, it was health care overhaul or bust, may the devil take care of the costs. On the other side it was an other-worldly insistence that what we presently have is working just fine, why fix it if it ain't broke?

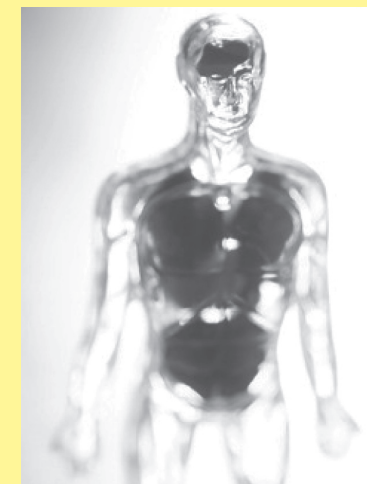
Every doctor knows that health care as it is presently configured has not worked in years. The cognoscenti also know that the current proposals flitting through congress will not significantly improve the situation. What we are presently debating is vote-hunting by any other name. It does not, in my opinion, go far enough. And it is anything but revolutionary. This is not the time for incremental cure.

Oscar Wilde, gadfly of Victorian letters and sensibility, memorably described fox hunting-that sport of princes- as the unspeakable in pursuit of the uneatable. In like manner, this health care bill has been smeared as the unpassable masquerading as the ineluctable. But doctor, beware: something will surely be passed by congress. It will probably be unspeakable, uneatable, unworkable, unviable- but it will be a bill, and therefore, the law of the land. Not adding our collective voices to the (deafening) fray, illustrate that we may appreciate, but grossly underestimate, the case against the *status quo*.

Insurance companies have already delivered a decapitating blow to the moral imperative of universal coverage. Wielding their favorite shibboleth, "pre-existing condition" to magnificent effect, wavering observers have been dragged down in the under-tow of fiscal prudence. Trial lawyers are darkly musing on (un)intended consequences of tort reform. You'd think by reforming health care, consulting clinics would be transformed into stalags. Not to be outdone, the talking heads have made hay in the melee. Using his own father's terminal illness as a prop, Keith Olbermann of MSNBC has declared a *fatwa* on apostates on the Democratic center, who are understandably nervous about the costs. Not to be outdone, Rush Limbaugh speaking from his moral redoubt on Mount Excess, has steadily cast stones at weak-kneed conservatives who think that health care in the richest country in the world might, after all, be a right rather than a privilege. The push-back from the left has been reciprocal and incendiary. Allusions have been made to prescription drug habits, Latina housekeepers, morbid obesity, juvenile drug use..... welcome to American politics. My take? Those who live in glass houses shouldn't get stoned.

See you Friday lunch-time, at the CME lounge.

*Beze Adogu, MD, Ph.D., FACP*



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## RESTLESS LEG SYNDROME

RLS refers to a familial, compulsive, nocturnal, posture-independent, leg movement, where rest discomfort is ameliorated by continuous lower limb movement. Patient descriptions are often misleading, and the sensation might be described as painful, arthritic, pruritic or tingling. Prevalence is higher in women, elderly, smokers and diabetics.

Early-onset RLS (primary RLS) starts before 45 years of age, and is generally milder, with an autosomal-dominant inheritance pattern. Late-onset RLS (secondary RLS) is more rapidly progressive and often associated with underlying medical disease.

Underlying causes may include renal failure, iron deficiency, pregnancy, chronic sleep deprivation, and treatment with anti-depressants or dopamine antagonists.

Differential diagnosis include: peripheral neuropathy (check for distal sensory perception and ataxia of gait), peripheral vascular disease (check for distal arterial pulses), nocturnal leg cramps, drug-induced akathisia (from neuroleptics).

Management: encourage restorative sleep, daily walking exercises, warm bath/stretch exercises before bed-time, quit smoking, limit alcohol/caffeine use, avoid anti-depressants (Bupropion SR is an exception), stop dopamine antagonists (e.g. Reglan, Haldol, anti-

### RESTLESS LEG SYNDROME (CONT.)

histamines, anti-emetics, anti-psychotics, etc), consider iron supplements (especially if iron saturation under 20% and ferritin level under 100), dopamine-agonist medications at approximately 15% of doses used in parkinsonism (carbidopa-L-dopa/Sinemet 25/100-50/200 mg p.o. 1 hour before onset of symptoms, ropinirole/Requip 0.25-6 mg p.o. at bedtime vs pergolide/Permax 0.1-1.0 mg p.o. daily vs pramipexole/Mirapex 0.125-1.5 mg p.o. at bedtime), low-dose anticonvulsants (gabapentin/Neurontin 300-2400 mg p.o. daily vs clonazepam/Klonopin 0.5-4 mg p.o. daily), low-dose opiates (tramadol/Ultram 50-400 mg p.o. daily).

In using any dopaminergic agent, the physician should monitor carefully for *rebound* (worsening of symptoms soon *after* usual dosing period, often whilst using short-acting agonists) and *augmentation* (worsening of symptoms *earlier* than usual onset, often whilst using higher drug doses) effects.

### MEDICATION ERRORS: A GROWING THREAT

An estimated 3000 drugs either look alike or sound alike with a risk of unintentional substitution. This avoidable error, affecting both generic and brand-name drugs, could be potentially fatal. Common mix-ups include *Azelex* (anti-bacterial agent) vs *Azilect* (anti-parkinsonism drug), *Ferro-Sequel* (iron supplement) vs *Seroquel* (anti-psychotic), *Klonopin* (sedative) vs *clonidine* (anti-hypertensive), *acetazolamide* (diuretic) vs *acetohexamide* (sufonylurea anti-diabetic) vs *Acetadote* (acetylcysteine) vs *acetohydramic acid* (urease antagonist), *phenytoin* (anti-convulsant) vs *phenobarbital* (anti-epileptic), *Norcuron* (neuromuscular blocker) vs *Natreacor* (recombinant ANP for heart failure), *Reminyl* (for dementia) vs *ramipril* (for hypertension) vs *Amaryl* (for diabetes), *disodium EDTA* (for hypercalcemia) vs *calcium disodium EDTA* (for heavy metal toxicity)...the list goes on. The solution is vigilance (spell out the drug) and asking the pharmacist to repeat the drug name after you.

### FIRST DOSE HYPOTENSION

Be wary of “first-dose” hypotension, a sudden unpredictable drop in BP, in patients starting anti-hypertensive drug treatment: the risk factors are dehydration, concurrent diuretic treatment, acute blood loss (or “priming” effect of hemodialysis and extracorporeal blood shunts) and high-renin phenotype.

### DIGOXIN TOXICITY

Digoxin treatment can provoke any cardiac arrhythmia, though atrial fibrillation (with slow ventricular response) and AV junctional tachycardia are the most typical. Patients at high risk for digitoxicity are the elderly, those with renal failure, electrolyte abnormalities (especially hypokalemia and hypercalcemia), systemic acidosis/hypoxemia, hypothyroidism and patients with cardiac amyloidosis.

### INFECTION SANS INFECTION

Consider fungemia in ICU patient with “culture-negative” inflammation: those at high risk are patients on prolonged antibiotic treatment, neutropenic, immuno-compromise (from malignancy, HIV, steroid or cytotoxic treatment), prolonged hyperalimentation and foreign body in-situ (especially Foley and IV catheters).

### INSOMNIA

Best defined as a *subjective* report of *insufficient* or *non-restorative* sleep despite adequate opportunities for sleep. Though common in the elderly, insomnia is not a normal consequence of aging. Insomnia is also prevalent amongst those under social stress. Treatment should only be started after underlying triggers (and situational factors) are explored and corrected, and drugs are best used for specified periods of time at the lowest effective dose required to control symptoms.

#### There are 4 major treatment groups:

1. Benzodiazepines (e.g. Xanax which reduce both REMs sleep and sleep latency, but may lead to rebound insomnia especially with extended use or after rapid discontinuation, and may lead to “hangovers” as well as a moderate tolerance and addiction potential).
2. Anti-depressants, such as trazodone 75 – 500 mg p.o. daily
3. Non-benzodiazepines are generally better tolerated and have fewer side-effects, binding either to w-1 benzodiazepine receptors such as Zolpidem 5-10 mg p.o. q daily, Zaleplon 5-10 mg p.o. q daily, or to GABA-A receptors such as zopiclone 7.5 mg p.o. q daily, eszopiclone 2 mg p.o. q daily, indiplon 20 mg p.o. q daily, or act as melatonin receptor agonists such as ramelteon 4-8 mg p.o. q daily
4. Herbs/Botanicals have been employed with variable success, using valerian, hops, chamomile, passion flower extract and kava-kava

### SHOULD WE TREAT PRE-HYPERTENSION?

Pre-hypertension is defined as systolic BP between 120-139 mmHg or a diastolic BP between 80-89 mmHg. Pre-hypertension is not benign, and is associated with double the cardiovascular morbidity in the normal population (Chobanian et al, Hypertension 2003). Proposed treatment is with an angiotensin receptor blocker (Julius et al, N England J Med, 2006). Too many physicians are still not treating pre-hypertension (Williams et al, J American Coll Cardiology, 2008). Reason: physician inertia.

### PSEUDO-SEIZURES: WHEN EPILEPSY IS NOT EPILEPSY

Pseudo-seizure refers to a paroxysmal non-epileptic episode of altered behavior including abnormal motor activity, altered sensation or abnormal perception. Pseudo-seizures are neurologic mimics of a profound emotional disturbance. Prevalence is estimated at 2-33/100,000 population, making it the most common cause of uncontrolled seizure activity, and onset is usually from young adulthood (though cases have been recognized in children and the elderly), 70% of cases are female, attacks are rarely unwitnessed (an audience is crucial), and at least 15% also have true underlying epilepsy. Suspect pseudo-seizures in epilepsy associated with: atypical triggers (such as pain, emotional distress or external cues); absence of significant injury (though skin abrasions and lacerations of tongue tip are common); episodes are refractory to drug treatment; history of antecedent psychiatric illness; multiple somatic complaints; normal neurologic exam; over-dramatization of attacks; atypical emotional overlay (such as anxiety, depression, indifference to attacks); atypical motor movement (as patients are not neurologists, they present what they think epilepsy should look like, which are typically neurologically implausible: side-to-side shaking of head, non-responsiveness, gaze diversion, non-synchronous motions, bicycling activity, exaggerated lordosis of back, weeping, tight eyelid closure).

**Differential diagnosis:** other causes of “queer turns” (i.e. organic non-seizures) such as TIA, syncope, migraine, paroxysmal cardiac arrhythmias and infantile breath-holding attacks.

**Diagnosis:** EEG-video recording is confirmatory; earlier attempts at biochemical diagnosis showing absence of seizure-related spikes in serum prolactin, CK, nerve specific enolase have been found lacking in sensitivity.

### TO TRANSFUSE OR NOT

Healthy *euvolemic* volunteers survive *isovolemic* anemia with hemoglobin as low as 5 g/dL, but experimental models suggest that this threshold is higher in coronary artery disease, possibly up to 10 g/dL. There is a higher mortality amongst ICU patients transfused to a hemoglobin above 8 g/dL, yet Jehovah’s witnesses who decline transfusion have a higher mortality with hemoglobin levels under 10 g/dL. Furthermore, transfusion with “aged” blood is problematic, being associated with rigid non-deformable erythrocytes, low levels of 2,3-diphosphoglycerate, cytokine release, reduced oxygen delivery and ultimately, tissue hypoxia. The emerging consensus is that the need for blood transfusion is really a surrogate index for severity of underlying disease: higher transfusion needs translate to worse underlying pathology and worse clinical outcomes.

### BARE METAL OR DRUG-ELUTED STENTS?

The Achilles’ heel of percutaneous coronary angioplasty (PTCA) include plaque disruption (leading to acute coronary occlusion and peri-procedural infarcts), restenosis (from neointimal hyperplasia and negative vascular remodeling) and bleeding complications. Drug-eluted stents were developed to impede neointimal hyperplasia, especially in high-risk groups such as diabetics and those with chronic total occlusions or small caliber vessels/bifurcating lesions. Still, drug-eluted stents are prone to (very) late stenosis occurring >30 days post-procedure, most of which are associated with a high fatality rate. Consequently, bare metal stents are still favored in: patients unlikely to comply with dual anti-platelet treatment for extended periods (either from poor compliance history, bleeding complications, socio-economic factors, drug allergy to Plavix/ASA or high probability of upcoming surgery); patients with ST-elevation acute MI; patients with limited life expectancy; and patients with either saphenous vein graft or large caliber coronary vessel (typically >4 mm diameter).

### SMOKING GUN

Smoking should be regarded as a chronic, relapsing disease which is especially resistant to conventional treatment. Smoking is the leading preventable cause of illness and premature death in the Western world, and a modifiable risk factor for progressive cardiovascular disease, chronic lung disease/COPD, malignancy, peptic ulceration, pregnancy-related complications and progressive kidney failure (especially in diabetic nephropathy and polycystic kidney disease). Smoking is the most powerful predictor of which hypertensives that go on to develop kidney failure. Smoking kills more Americans *per annum* than World War I, World War II and the Vietnam conflicts combined, reflecting an estimated 18-20% of stroke-related deaths, 20-25% of cardiac deaths, and 30-33% of cancer deaths. An estimated 23% of adult males and 19% of adult women currently smoke in this country.

The pathophysiologic basis of nicotine addiction is not fully understood, but studies indicate a huge dopaminergic surge in the *nucleus accumbens* during smoking. All therapy must incorporate both situational, drug and behavioral remedies. Today’s smoker started earlier, is more addicted, and is also more treatment-refractory than his/her peers of 3 decades earlier. There are over 45 million smokers in the United States, using an average of 25 sticks of cigarettes/day, and though 41% try to quit each year, less than 10% are ultimately successful.

The first medical intervention in any smoker, irrespective of his/her other complaints, would be to help him/her quit smoking. **There are 7 facets in a successful intervention program:**

1. Choose a “quit date”, which should be a psychologically meaningful date for the patient (such as an anniversary or birth date);
2. Substitute a slow-delivery system for nicotine to blunt withdrawal responses (nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine transdermal patch);
3. Consider adding a partial agonist at nicotine receptor such as Chantix/Varenicline 0.5 mg p.o. qd titrating upwards to 1 mg p.o. BID, which acts at the a4b2 nicotine receptor;
4. Consider dopaminergic mediators such as Zyban/Bupropion SR starting at 150 mg p.o. q daily x 3 days, going up to 150 mg p.o. BID over 1-2 weeks;
5. Provide family or peer support, either individually or in a group setting;