Athens Kidney Center
1440 North Chase Street
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RETURN SERVICE REQUESTED

INSOMNIA: DOCTOR, I CAN'T SLEEP

Sleep as well as wakefulness are tightly regulated physiologic processes, governed by circadian and homeostatic patterns. Sleep is thought to be predicated by gabaergic and galaninergic projections of the ventrolateral preoptic nuclei of the anterior hypothalamus which send inhibitory impulses to the tuberomammillary nuclei and brainstem arousal regions to impede wakefulness. Insomnia is described as recurrent difficulties with either the initiation, maintenance, duration or quality of sleep despite conducive circumstances of time and opportunity. Treatment may be cognitive-behavioral or pharmacologic. Pharmacologic therapy includes:

1. Benzodiazepines: shorten latent period before sleep onset, prolong first 2 stages of sleep, and shorten duration of deep non-REM sleep; avoid triazolam (Halcion) which may trigger anterograde amnesia; avoid long-acting benzos which bear a high risk of day-time somnolence; avoid benzos which undergo CYP3A4 metabolism, which is virtually all benzos except lorazepam/oxazepam/temazepam (reduced drug effect with CYP3A4 inducers, potential drug toxicity with CYP3A4 inhibitors): choice is between oxazepam 10-30 mg p.o. QHS or lorazepam 0.25-4 mg p.o. QHS or tamazepam 7.5-30 mg p.o. QHS.
2. Benzodiazepine (GABA-a) Receptor Agonists: rapid-acting sleep inducers which are metabolized by CYP3A4 though clinical significance appears limited: choose either short-duration zolpidem (Ambien) 5-10 mg p.o. QHS or zalepion (Sonata) 5-20 mg p.o. QHS vs. intermediate-duration eszopicione (Lunesta) 1-3 mg p.o. QHS.
3. Other Drugs: (a) the melatonin agonist, ramelteon (Rozerem) 8 mg p.o. QHS, which only slightly reduces sleep latency by ~12 minutes but has no addiction risk; (b) anti-histamine drugs, diphenhydramine (Benadryl) and doxylamine (Unisom), which are useful for short-term use but risks rapid development of tolerance to sedative effects, dry mouth/blurred vision/prostatism from anti-cholinergic effects, and day-time sedation; (c) sedating antidepressants, including trazodone, amitriptyline, mirtazapine and doxepin; (d) the homeopathic remedy, valerian root, is very safe but also very ineffective (Taibi et al, *Sleep Med Rev*, 2007)

DIAGNOSTIC CHECK-LIST: RECURRENT SEVERE HYPOGLYCEMIA

Diagnosis of hypoglycemia is based on random glucose level <70 mg/dL, and "severe" hypoglycemia is diagnosed if hypoglycemic event requires assistance, including alteration in cognitive status. Hypoglycemia may be "asymptomatic" due to (hypo)glycemic unawareness, which may be a reflection of long-standing diabetes/neuropathy, nocturnal hypoglycemic occurrences (suspect in diabetic patient with recurrent nightmares, unexplained early morning fatigue/headaches, depression, new-onset seizures, night sweats, morning hypothermia, elevated night-time urine cortisol/creatinine ratio), medication-related adversity (such as beta-blockers) and repetitive hypoglycemic episodes.

Etiology commonly from excessive/unphysiologic hypoglycemic drug or insulin dosing, which may be systematic (fault may be MD or patient's or environment) or erratic (usually accidental- memory lapse, visual misinterpretation,misidentification of drug/vial, wrong injection site into muscle/fat deposit). Other causes: (**1**) drop in endogenous glucose from liver disease, kidney failure, adrenal failure, hypopituitarism, severe hypothyroidism, alcoholism; (**2**) drop in exogenous glucose from skipped/delayed meals, malabsorption, pancreatitis, gastroparesis; (**3**) increase in glucose utilization (unaccustomed exertion, fever/critical illness, parasitoses/malaria, seizures, insulinomas/mesenchymal tumors); (**4**) increase in insulin sensitivity (medication-related and recent weight loss); (**5**) reduced insulin elimination (renal failure); (**6**) psychiatric adversity, including factitious hypoglycemia;

the
SECOND OPINION

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FROM THE EDITOR

Economic turmoil makes for strange bedfellows, often providing headwinds for public unrest. Take the Occupy Wall Street movement, an effervescent group of diverse interests and competing claims, whose stated aim is nothing short of "fiscal revolution". Strong words, but then, their we-against-them brand of populist agitprop has been embraced by Tea-Party conservatives, libertarians as well as notable "champagne liberals" of the Left. Sadly, this well-intentioned populist movement, like others before it, will soon fizzle out as its fiery energy is doused by the passage of time, inclement weather, social obligations and inertia. Political agitation is a bit like Alice in Wonderland: you have to run with all your strength just to stay in the same spot. Successful political protest in stable democracies is obliged to choose between making a loud noise or staging a small action, but not both. By electing to do both, OWS was destined to implode from within. Even as this strange season of anomie moves through Wall Street back to Main Street in televised and often unruly gestures of protest and defiance, it has left our political culture with a new shibolleth: are you in the 1 percent or amongst the 99 percent?

The American ethos, a throwback to *fin de siecle* Victorian morality, had always minimized the social impact of personal wealth. The American dream was the democratization of opportunity- a noble, if illusionary, precept founded on the notion that black ink, not blue blood, was the means to national redemption. The rich were reticent, the poor were resigned, whilst the middle class aspired. Earned wages were shared out amongst colluding interests: the Church in tithes, government as taxes, schools in fees, to our conscience in charitable donations, and the rest for a pittance. Nobody complained, because there was a perception of shared sacrifice and suffering. That tacit assumption of overall equality greased our social contract.

That is, until the dams broke with the floods of economic recession. This economic crisis, like all other crises before it, was in need of a malefactor, who has since been identified as the top 1 percent-whover s/he is. A recent *NY Times* article by Jeremy White et al, provides a working taxonomy for the 1 percent: they have a total household income of $383,000 or more (somewhat less if you live in the Mississippi delta, significantly higher if your zip code is 90210), had attended 4-year colleges (where they disproportionately majored in either Biology, Economics, Engineering, Business or Accounting), and are generally workaholic (routinely pulling down 50 hours or more each workweek). They also own 35% of the nation's gilded assets (though somewhat deceptively, they only earn 19% of the country's overall pre-tax income) and tend towards the conservative in ideology and precept. That is the face of our common enemy.

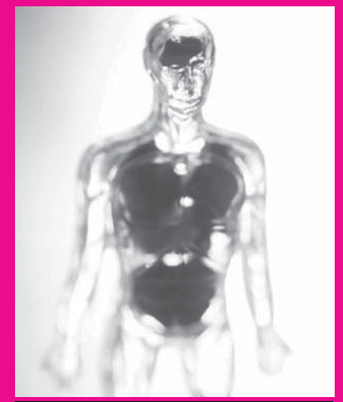
Guess what? It turns out that the enemy is us. Despite the ennui of practising physicians everywhere, who have been dying in installments over the pragmatic indecision of government regarding proposed Medicare reimbursement cuts, doctors are the largest group of 1 percenters in this country. Physicians occupy the largest bloc of 1 percent fiefdoms- more than CEOs, managers, professional athletes, politicians, lawyers and engineers. A full 27 percent of physicians working in offices and clinics are in the top 1%, as are 21% of physicians in general health services, 19% of doctors working in colleges and tertiary institutions and 17% of hospital-employed physicians. Of course, the likelihood of attaining 1 percent depends too on your chosen specialty: does it utilize mostly procedural or cognitive skills? No other profession comes even close. Next time you feel like complaining about how unfair it all is, or worse, throwing in your lot with the OWS crowd, remember our tribe is part of the chosen 1 percent.

I'll see you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, PhD, FACP

EXCESS RISK OF STROKES WITH ARANESP: YES, BUT WHY?

Erythropoesis-stimulating drugs, such as Aranesp, have been employed for treating chronic anemia in CKD, cancer and other conditions. Whilst anemia is associated with a higher morbidity and mortality in these patients, the CHOIR study (Ajay Singh et al, *N Engl J Med*, 2011) first highlighted a 34% increase in the primary end-points of stroke, heart failure, MI and death when higher hemoglobin targets were adopted. The recent TREAT trial (Trial to Reduce cardiovascular Events with Aranesp Therapy) by Skali et al, *Circulation*, 2011, confirms an increased risk of stroke whilst on Aranesp treatment in a cohort of patients with diabetes mellitus, non-dialysis CKD and anemia. However, this heightened risk was not associated with any identifiable characteristic such as hemoglobin level, blood pressure, platelet count or drug dosage. Take home message: erythropoietins are effective for anemia management but at a huge risk, *caveat emptor*.



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HARBINGER OF ICU DEATH: REDUCED MYOCARDIAL BLOOD FLOW IN ACUTE HYPOGLYCEMIA

Omar Rana et al, *Circulation*, 2011, looked into the unexplained excess in cardiovascular mortality associated with sudden hypoglycemia in diabetes mellitus. Hypoglycemia is common, afflicting a third of insulin-treated diabetics within the previous year, and at least 10% of hospitalized patients treated with sliding scale insulin in the ICU setting. Also, severity of acute hypoglycemia is strongly linked to likelihood of cardiac death in the 2 years following the acute hypoglycemic event. In this UK study, twenty-eight diabetic subjects and nineteen healthy volunteers were recruited for insulin clamp studies, where hypoglycemia was pharmacologically induced whilst undergoing real-time myocardial contrast echocardiography with low-dose dipyridamole. Myocardial blood flow reserve was found to be relatively low in diabetics especially those with microvascular complications, and myocardial blood flow reserve further decreased acutely during hyperinsulinemic hypoglycemia amongst diabetic and control subjects, suggesting a possible pathophysiologic link between hypoglycemia and increased cardiac deaths.

DISCRIMINATION IN THE ICU: HEIGHT NOT GENDER IS KEY

The nuances of LPV (lung protective ventilation) in the ICU are multiple: for the non-expert, it is sufficient to emphasize that it does improve survival and time on mechanical ventilation following acute lung injury. Han et al, *Crit Care*, 2011, studied 421 patients with acute lung injury following sepsis. Women were found to be less likely to receive LPV for acute lung injury (46% as opposed to 59%), despite having similar baseline characteristics as their male counterparts, besides a worse illness severity and shorter stature. It makes little sense that the sickest were more likely to be denied potentially life-saving technology, therefore it does appear that the discriminant culprit factor here is short stature. In the ICU? The authors (rather tongue-in-cheek, I imagine) suggest strategies to harmonize application of LPV regardless of height.

MANAGING SIDE EFFECTS OF OPIATE USE IN ICU

Opiates are commonly used for effective pain control in the ICU. However, unwanted side-effects may limit tolerance to this class of drugs and undermine therapeutic efficacy.

1. Nausea & Vomiting: consider secondary organ failure and opiate-induced pseudo-obstruction (colonic constipation); consider using different medication groups in combination- antihistamines + anticholinergic drugs + steroids + Reglan + benzodiazepines + antidepressants
2. Respiratory Depression: resuscitate with IV naloxone (Narcan) and reduce opiate dose by 25-75%
3. Hyperalgesia: reduce or wean off opiate + substitute another opiate class + consider another analgesic drug + add NMDA antagonist (ketamine or methadone)
4. Delirium: reduce opiate dose + add neuroleptic agent (Seroquel or Zyprexa often effective) + consider adding benzodiazepine as adjuvant
5. Constipation: symptomatic therapy (p.o. fluids, increased dietary fiber, prune juice, low-dose bulk laxatives) + laxatives/carthartics + methylnatrexone (Relistor) 8 mg sq Q alternate days x 2 doses
6. Myoclonus: reduce opiate dose + clonazepam (Klonopin) + consider valproate (Depakote) or baclofen (Lioresal) or dantrolene (Dantrium) in refractory cases
7. Undue Sedation: consider epidural opiate route + consider switch to different opiate class + consider methylphenidate (Ritalin) or modafinil (Provigil) or dextroamphetamine (Dexedrine) in refractory cases

FLESHING OUT RENAL ARTERY STENOSIS: HERE ARE THE MAIN POINTS, AGAIN

David Lao et al, *Mayo Clin Proc*, 2011, provide a timely and balanced overview of the now-controversial treatment for renal artery stenosis syndrome (renal arterial obstruction caused chiefly by ostial/proximal atherosclerosis, and rarely by fibromuscular dysplasia, vasculitis, radiation arteritis, extrinsic compression, neurofibromatosis or congenital bands) which can lead to ischemic nephropathy (accounting for 14% of new ESRD cases [Harding et al, *J Am Soc Nephrol*, 1992] and suggested by >1.5 cm discrepancy in renal size or worsening azotemia following ARB/ACE inhibitor therapy), resistant arterial hypertension (especially in the young, i.e. <30 y.o., or elderly, i.e. >60 y.o.), unstable cardiovascular syndromes (including unstable angina and"flash" pulmonary edema) and recurrent "idiopathic" congestive cardiac failure. Diagnosis is based on renal ultrasound (85% sensitivity, 92% specificity) or CT angiography (94% sensitivity, 60-90% specificity) or MR angiography (95% sensitivity, 95% specificity) with the following caveats: ultrasound is heavily operator-dependent and proper interpretation of wave-forms can be difficult for operators; CT angiogram risks contrast allergy/nephrotoxicity, involves radiation exposure, and often creates artifact within calcified vessels; MR angiogram has limited spatial resolution making assessment of smaller/accessory arteries difficult, risks nephrogenic systemic fibrosis in patients with advanced CKD, and cannot be used in patients with cardiac/cochlear or spinal implants or in patients who are claustrophobic or who have short image acquisition times (because they cannot hold their breath for extended periods). Treatment is universally medical: anti-hypertensive management with ARB/ACE inhibitor, high-dose statin treatment, smoking cessation and glycemic control. Therapeutic revascularization (by balloon angioplasty or stenting) should be reserved for patients with hemodynamically-significant lesions (defined as >70% luminal stenosis or trans-lesional arterial pressure gradient >20 mmHg) who are non-compliant or refractory to optimal medical therapy or in patients with unstable cardiovascular syndromes (including resistant hypertension and "flash" pulmonary edema) in the absence of advanced renal disease (which is in turn suggested by renal atrophy or proteinuria >1 g/day or arterial resistive index >0.8, and less reliably by elevated serum creatinine levels).

MIXING NSAIDs WITH CARDIAC DISEASE: IKKE

Olsen et al, *Circulation*, 2011, harnessed the awesome power of Denmark's electronic medical registry in tracking patients with previous acute MIs who were hospitalized between 1997 and 2006. Recurrent MIs were correlated to NSAID use: NSAID use increased the odds of recurrent MI or death by 45% within the first week of use, and 55% if treatment lasted up to 3 months. Diclofenac was the worst culprit. There was no safe therapeutic window: all NSAIDs were bad, some were worse than others, but Naproxen was the safest at low doses; even short-term NSAID use, only taken for a week or less, was potentially lethal in this population; Diclofenac was associated with higher cardiac risk than certain banned COX-1 antagonists. So why are NSAIDs still obtainable as OTC remedies?

MAKING THE DIGNOSIS: WHAT MATTERS, WHAT DOESN'T

An emergency department study by Paley et al, *Arch Intern Med*, 2011, provides answers to some clinical conundrums: senior medical residents (diagnostic accuracy 80.1% with average evaluation time of 40 mins) have the same diagnostic capacity as 20-year hospitalist veterans (diagnostic accuracy 84.4% with average evaluation time of <25 mins); proper diagnosis was dependent on history alone in 19.5% of cases, physical examination alone in 0.65% of cases (ouch!), history plus basic lab tests in 14.7% of cases, history and physical exam in 39% of cases, history and physical exam and basic lab tests in 17.7% of cases, and imaging studies in 6.3% of cases.

PLEIOTROPY OR MAGIC: STATIN THERAPY HELPS FLU PATIENTS

A recent observational study by Vandemeer et al, *J Infect Dis*, 2012, shows that statin treatment was associated with reduced mortality amongst hospitalized flu patients. The pleiotropic effects of statins are well known: anti-inflammatory, immuno-modulatory, anti-atherogenic, et cetera. Now comes further evidence that statins may play an adjunctive role in treating acute infections. Using the CDC Emerging Infection Program, influenza hospitalizations across 10 states were studied during the 2007-2008 flu season. Over 3000 patients were identified, of which a third were on statins before or during hospitalization. After adjusting for age, race, vaccination status, antiviral regime and co-morbidities, it was found that statin use was associated with a 41% reduction in mortality. It should be pointed out that most statin users were elderly Caucasian males with chronic pulmonary-cardio-renal disease, but were also significantly more likely to have previously received flu vaccines. Whilst inconclusive, this study does suggest that combining statins with anti-viral drugs may reduce influenza-related mortality. Now for a blinded, randomized trial to "nail" this issue....

DABIGATRAN AND INCREASED RISK OF HEART ATTACKS

The first major assault on dabigatran (Pradaxa), a direct thrombin inhibitor, was opened at the meta-analyses front last month. In a paper based on 7 randomized clinical trials covering 30,154 participants who had used dabigatran for stroke prophylaxis in atrial fibrillation (2 studies), acute venous thromboembolism (1 study), acute coronary syndrome (1 study) and short-term DVT prophylaxis (3 studies), Hernandez & Uchino, *Arch Intern Med*, 2012, found that dabigatran was linked to a higher incidence of acute MI or acute coronary syndrome when compared to controls (who had received either warfarin, enoxaparin or placebo). There was a 33% higher relative risk of MI or acute coronary syndrome in dabigatran recipients though the absolute risk itself increased only by 0.27%. It is therefore very suggestive that dabigatran either increases cardiac risk (less likely) or lacks the protective effect of warfarin/heparinoids (more likely).

AFTER 13 YEARS AND NO BENEFIT, IS PSA SCREEN DEAD?

Andriole et al, *J Natl Cancer Inst*, 2012, released the prostate component of the PLCO (prostate, lung, colorectal, ovarian) cancer screening trial, and it wasn't pretty. Mortality after 13 years of follow-up in 76,685 men, aged 55-74 years, who had been randomly assigned to intervention regimen (annual PSA screening x 6 years and annual digital rectal rectal exam x 4 years) vs control regimen (usual care, sometimes including opportunistic screening). Relative risks were assessed as ratio of observed rates (of incident prostate cancers and death from prostate cancers) in the intervention and control arms. About 57% of study participants were followed through 13 years and 92% for 10 years only. Cumulative incidence rates for prostate cancer was 108.4 per 10,000 person-years in the intervention group and 97.1 per 100,000 person-years in the control group, reflecting a 12% relative increase in the intervention arm. After 13 years follow-up, the cumulative mortality rates from prostate cancer were 3.7 and 3.4 deaths per 100,000 person-years in the intervention and control arms respectively. The difference was not statistically significant. Summary: prostate cancer screening increases diagnosis but does not significantly affect mortality.

STROKE MIMICS IN THE ED: CAUTION BEFORE THROMBOLYSIS

Acute ischemic stroke is a medical emergency which treatment relies on quick and accurate clinical (not radiologic) diagnosis followed by immediate thrombolytic treatment. Ville Artto et al, *Ann Emerg Med*, 2012, reviews the problem of intravenous thrombolytic therapy (tissue plasminogen activator) mistakenly administered for "stroke mimics" in the Emergency Room, a situation thought to occur in 1.3 to 13% of acute stroke presentations. Stroke mimics were younger, more commonly female, generally lacked common vascular risk factors (such as previous heart failure, atrial fibrillation, peripheral artery disease, TIAs), but were otherwise demographically indistinguishable from neuroimaging-negative stroke patients. Common stroke mimics were: epileptic seizures, complicated migraines, demyelinated diseases, encephalitis and conversion disorders.

NEW STRATEGIES FOR TTP: TARGETING THE B-CELL

Thrombotic thrombocytopenic purpura is a rare and enigmatic clinical diagnosis based on demonstrating a pentad of features: fever, Coomb's negative microangiopathic hemolytic anemia, renal failure, thrombocytopenia and non-focal neurologic deficits/altered mental status. Its pathophysiology involves functional inactivation of the metalloproteinase, ADAMTS-13, often by its being bound by an inactivating (acquired) immunoglobulin, hence failing to cleave von Willebrand factor (vWF) multimers and allowing those multimeric proteins to incite platelet aggregation and diffuse intravascular thrombosis. Treatment has traditionally been by plasmapheresis, designed to remove circulating (acquired) immunoglobulins from the systemic circulation, with or without adjunctive steroids. Relapsing or refractory disease are often treated with cytotoxic drugs such as Cytoxan or vincristine. Now comes a third option, the chimeric monoclonal anti-CD20 antibody, Rituximab, which attacks mature B-cells which express the epitope but not long-lived plasma cells (which do not) as reported by Froissart et al, Crit Care Med 2012. This new strategy was quick-acting, effective, well tolerated, and apparently obviates the need for last-ditch splenectomy. However, as Vasileios Kyttaris, MD, cautions in an accompanying editorial, we've been down this road before: Rituximab showed promise against SLE in observational studies, but drew a blank in head-to-head blinded comparisons against placebo in randomized studies (Merrill et al, *Arthritis Rheum*, 2010).

COGNITIVE DECLINE IN CKD: COMMON VASCULAR MECHANISMS

Helmer et al, *Neurology*, 2011, report on the longitudinal relationship between chronic kidney disease/microalbuminuria and cognitive decline/dementia as part of the long-awaited 3C study. Using a CKD population cohort of 7,839 patients aged >65 years and followed over 7 years, global cognitive function was assessed using the mini-mental state examination (MMSE) and screens were performed for incident dementia. Baseline kidney function was not associated with increased dementia risk or cognitive decline over 7 years. However, rapid fall in kidney function (by 4 mL/min/1.73 m[2]/year) over the first 4 years was associated with a 5.35x higher risk of vascular dementia and higher cognitive decline compared to more slowly progressive kidney failure. Proteinuria was also associated with a higher risk of vascular dementia.

FAILURE (AGAIN) OF N-ACETYLCYSTEINE: SO WHAT ABOUT OXIDATIVE STRESS?

The prognosis of severe alcoholic hepatitis is bleak: a third of patients will die within 6 months, regardless of treatment. Prednisone is the mainstay of treatment, and adding N-acetylcysteine appeared a sensible option, in this unintentional reprise of the contrast-induced nephrotoxicity story. In a randomized trial with 174 participants, Eric Nguyen-Khac et al, *N Engl J Med*, 2011, found that adding IV N-acetylcysteine (Mucomyst) to steroids decreased 1 month mortality (8% vs 24%) but did not improve 3-month or 6 month survival rates. However, adding IV Mucomyst did reduce infection rates as well as the incidence of hepato-renal syndrome. A multivariate analysis showed that survival at 6 months was linked to young age, less dyscoagulopathy (shorter prothrombin times), and lower baseline bilirubin level (or drop in serum bilirubin level by day #14). As with other comparative trials of Mucomyst, the authors seek the silver lining in the clouds: maybe a more powerful trial or longer duration of Mucomyst administration will do the trick?