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William R. Ware, PhD - Editor

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The emphasis in this issue is on diabetes and cardiovascular disease. The conventional wisdom considers diabetes to be a risk factor for coronary heart disease on a par with pre-existing cardiovascular disease, but this is currently the subject of debate. Once diabetes is present, many physicians view the now high risk of heart disease as a justification for the prescription of statin drugs, in particular if there are other risk factors, a not uncommon situation given the weight given to age and the widespread prevalence of hypertension.

Since coronary atherosclerosis is normally a prerequisite for the eventual occurrence of an acute coronary event, the question arises concerning the evidence that cholesterol is related to the prevalence and progression of coronary atherosclerosis in diabetic individuals, since this is not the case in non-diabetics. In addition, how many diabetic individuals without any manifestation of coronary heart disease must be treated with statins in order to prevent one fatal or non-fatal heart attack? This issue will address these questions.

In addition, there is the ongoing controversy regarding intensive therapy with statins, anti-hypertensive drugs, aspirin and various blood glucose control drugs for the prevention of first cardiovascular events in screen-detected diabetics. The results are not impressive.

We also discuss the impact of smoking on coronary heart disease in men compared to women and the risk apparently associated with red meat and the risk of type 2 diabetes. Chocolate is also in the news again in the context of cardiometabolic disorders.

Finally, to assist in gaining perspective, this issue contains a short summary of the extent to which fines and lawsuit settlements impact Big Pharma.

Also included in this issue is a research review concerning what are called neuroenhancers, and what the critics call "Botox for the Brain." This is an important subject because we appear to be on the threshold of a major adventure into this brave new world of chemical manipulation of the brain in healthy individuals merely in the hope of enhancing performance and making them smarter and better able to compete. There are serious ethical and medical issues which must now be considered.

In closing then, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

CORONARY HEART DISEASE IN DIABETICS. ARE STATINS REALLY THE EVIDENCE-BASED ANSWER FOR PRIMARY PREVENTION?

Diabetes has reached epidemic proportions with about 200 million individuals worldwide affected and in the U.S. 1.3 million new cases diagnosed each year. Cardiovascular complications including coronary heart disease (CHD) are leading causes of mortality and morbidity among individuals with type 2 diabetes, which is by far the most common form of the disorder. The prevalence of CHD is found to be as high as 65% in diabetics referred for stress testing and the 10 year mortality in diabetic patients with known CHD is in excess of 70%.

In 2011, the American Diabetes Association published their view of the standards of medical care for diabetes.[1] Under prevention and management of complications, they discuss hypertension, blood lipids, antiplatelet therapy and smoking cessation. Central to the lipid management recommendations is the focus on LDL cholesterol and the recommendation of statin use by almost all diabetics. Thus it is of interest to examine the evidence for this central role of LDL and the magnitude of the benefits associated with statin use both in diabetic patients with and without cardiovascular/coronary heart disease.

CORONARY ARTERY CALCIFICATION PREVALENCE STUDIES IN DIABETICS

A number of studies have been published recently that find LDL is not a factor in the prevalence of coronary artery calcium (CAC) in diabetics as measured by electron beam tomography or coronary angiographic computed tomography.

- Mazzone *et al*. (CHICAGO study)[2] examined the prevalence of CAC in type 2 diabetics. They excluded type 1 diabetics and anyone with CAD, cerebrovascular or peripheral vascular disease, heart failure, very high triglycerides (TGs) or BMI >45. Lipoprotein determinants of the coronary artery calcium score (CACS) were HDL, TG, ApoB, non HDL and LDL cholesterol components called triglyceride rich Lipoproteins (TRL) In a multivariate analysis, significant factors were *age,* systolic blood pressure*,* sex, race, and TRL. LDL was not significant in the multivariate analysis.
- Anand *et al* examined factors associated with the prevalence of CAC in Type 2 diabetics.[3] They excluded subjects with documented CAD, atypical angina, abnormal ECGs, cerebrovascular or peripheral artery disease, or renal impairment. Multivariate analysis predictors of CAC were age, male gender, ethnicity, hypertension, duration of diabetes, statin use and UKPDS risk score. The input data set included hyperlipidemia which failed to appear in multivariate analysis. UKPDS is similar to Framingham risk score.
- Elkeles et al. studied the association between CAC and conventional risk factors in individuals with type 2 diabetes.[4] Subjects had no known CHD. Multivariate analysis yielded waist-hip ratio, systolic blood pressure, male gender and statin use. Factors which did not appear as significant in multivariate analysis included non-HDL cholesterol, LDL, cholesterol ratio, TGs and HbA1c. Thus while 36% were taking statins, no lipid or lipoprotein parameters emerged as significant in multivariate analysis.
- Wolfe *et al* also examined the association between CAC and traditional risk factors.[5] They found in a study of 71 diabetics with no evidence of CHD that the extent of CAC in was independent of LDL levels in an adjusted model. Age, male gender and BMI were the only significant factors.
- A study by Martin et al (Penn Diabetes Heart Study) examined factors associated with CAD in type 2 diabetics with no clinical evidence of CHD.[6] Only white individuals were enrolled. Analysis found only ApoB as a significant factor and in particular LDL was not significantly

associated with CAC after adjustment for age, sex, medications, hypertension, smoking, alcohol, exercise, family history of premature CVD, C-reactive protein and the metabolic syndrome.

- A Japanese study has also examined the association of the prevalence and extent of CAC with insulin resistance in chronic kidney disease patients free of symptomatic CVD or any history of previous heart attack.[7] CAC was measured by computed tomography. It was found that CAC becomes more prevalent and severe with an increase in the severity of kidney disease. In a multivariate analysis or factors associated with CAC, only the common measure of insulin resistance (HOMA-IR) exhibited a significant correlation. In the univariate analysis, all the classical lipid parameters failed to achieve significant association with the CACS, with LDL the weakest. Of the 111 subjects, 38 (34%) had type 2 diabetes although none used insulin.

These studies involving diabetic subjects raise a serious issue concerning LDL as a target for therapy in asymptomatic individuals since atherosclerosis is almost always a prerequisite precursor for eventual acute coronary and other vascular events.

CORONARY ARTERY CALCIFICATION PROGRESSION STUDIES IN DIABETICS

When coronary calcification is present, it almost always progresses with every increasing risk of acute cardiac events. Are LDL levels associated with the risk of progression of CAC in type 2 diabetics with no symptoms of heart disease? The answer based on the following studies appears to be no.

- A substudy of the Veterans Affairs Diabetes Trial examined the progression of CAC in 189 type 2 diabetics[8]. CAC progression was found in > 75% of subjects but was not influenced by standard risk factors and in particular, blood lipids were not significant. The albumin to creatine ratio, a marker for kidney problems, and lipoprotein-associated phospholipase (LP-PLA2) predicted progression independent of adjustment for age or other traditional risk factors. LP-PLA2 has also been associated with the progression of subclinical atherosclerosis in a study involving individuals either with or without type 1 diabetes.[9]
- A recent study examined CAC progression in a group of 398 type 2 diabetics.[10] In the final multivariate analysis, odds ratios for independent factors for progression of CAC were baseline CAC > 400 mm^3 (OR = 6.38), HbA1c > 7 (OR =1.95), and statin use (OR = 2.27), but not hyperlipidemia or smoking status. It is noteworthy that the researchers found statin therapy failed to inhibit progression of CAC but rather accelerated it. An earlier study from the same group found that 53% of a diabetic cohort had subclinical CAC. One-third of these had progression during 2.5 years follow-up. The increase in risk of progression was 212% greater for statin-treated patients with LDL < 2.6mmol/L compared to those untreated.
- Progression of atherosclerosis over 4 years measured by CAC was also addressed as part of the PREDICT study.[11] The rate of change was strongly related to baseline CACS and also independent, of CACS, correlated positively with waist to hip ratio, male gender, the use of antihypertensive drugs or statins and the albumin to creatine ratio. There was no relationship with traditional lipid risk factors, including LDL
- Compared to the above, somewhat different results have been reported.[12] The study excluded individuals with cardiac symptoms or known CAD including revascularization, stroke or peripheral vascular disease. Two EBCT scans were done with a mean of 27 months between. Baseline hypercholesterolemia, defined as using cholesterol-lowering drugs or having total cholesterol ≥ 240 mg/dL (6.2 mmol/L), was not found to be a significant risk factor. For the statin non-users, progression was at a median annual rate of 20% (4% to 44%) whereas for statin treated patients it was 10% (4% to 25%) No statistical analysis was included. The wide range suggests that these results should be viewed with caution.
- It is well know that depression is a comorbid condition associated with diabetes and depressive symptoms are a risk factor for CHD.[13] A recent report documented this in midlife women in the

SWAN Heart Study, where depressive symptoms were independently associated with progression of CAC.[14] In a multivariate analysis, the only other predictors of significance for progression were systolic blood pressure, and a low level of education. LDL was not a significant factor.

- Insulin resistance has been independently associated with the progression of CAC. In a CAC progression study based on the Kaiser Permanente of Northern California database, Lee *et al* [15] studied this issue. In the univariate analysis, TC, LDL, HDL and TG were not even close to being significantly associated with progression over 2 years of follow-up. In multivariate analysis, progression was associated with age, female gender, African Americans, diabetes, fasting insulin, dyslipidemia (presumably high TGs and low HDL), hypertension, diastolic BP and pulse pressure but not with lipid lowering medication.

Thus one is again prompted to question why LDL is a target for diabetics free of CHD when it has no influence on atherosclerosis progression.

CHOLESTEROL, DIABETES AND ACUTE CORONARY EVENTS. PRIMARY PREVENTION

If one examines the 2011 ADA standard of care.[1] four lipid lowering studies are cited where it is possible to stratify by both diabetes and the presence or absence of CHD and CVD, thus obtaining information on the role of statins in risk reduction for CHD in the context for primary prevention of type 2 diabetes. Their Table 11 indicates endpoint restriction to fatal CHD and non-fatal heart attack, but it is extrapolated to 10-year risk. It is thus of interest to look at the individual primary prevention studies. The results were as follows for absolute percent risk reduction for fatal and non-fatal heart attack and numbers needed to treat (NNT): ASCOT [16], 0.18%, 555; ASPEN [17], 0.7%, 142; CARDS [18], 2.0%, 50; HPS (MRC/BHF) [19], 3.2%, 31. HPS used 40 mg simvastatin; the other studies all used 10 mg atorvastatin. The CARDS results differ from that cited by the ADA paper, but the above numbers are derived directly from the original data.

The large difference between the absolute risk reduction in HPS compared to the other three, when the endpoint is fatal CHD or non-fatal heart attack can be explained by the inclusion in the diabetic group of individuals with arterial disease, including 33% with previous heart attack or other CHD and 18% with other occlusive artery disease. HPS only stratifies diabetics by prior CHD when the endpoint includes coronary events, all strokes, and coronary and non-coronary revascularization, which increases the benefit dramatically. Thus if primary prevention of fatal and non-fatal heart attacks is the issue, we are left with ASPEN, ASCOT and CARDS, all of which have low absolute benefits and large numbers needed to treat (NNT).

This weak association with large NNT is generally what has also been found in studies of non-diabetics which were rigorously restricted both to primary prevention or further restricted to low suspected level of bias.[20] Absolute risk reductions for major CHD events ranged from 1.0% (11 studies) to 1.3% (7 studies) and NNT from 100 to 77. There was no significant impact on mortality. Then there are the statin adverse effects. For liver dysfunction, cataract and myopathy, the number needed to harm with statin therapy has been estimated for men at 142, 52 and 81 and for women 136, 33 and 259, respectively.[21] It is doubtful that cataracts disappear if statin therapy is terminated. It is also strongly suspected that adverse events are significantly under-reported, downplayed or actually suppressed. Conservative clinicians might conclude that the treatment was not justified [20]. It appears clear that it is time for a new paradigm.[22]

Recently published observational studies, including one that looked at event-free survival, also find no association between LDL and CVD/CHD events in diabetic individuals [23,24]. A recent review even suggested that type 2 diabetes should not be considered a true risk equivalent for CHD [25].

Once diabetes and CHD present together, considerably larger benefits of lipid lowering with statins are observed and there is little disagreement regarding their use as standard treatment [1]. This same situation exists with non-diabetics. However, there is growing concern that most of the impact of statin drugs

involves pleiotropic effects, of which there is a long and impressive list containing actions that can influence acute events and have nothing to do with lipid lowering [26-28].

CONCLUSIONS

Thus the obvious question. Does targeting LDL in diabetics make any sense when it rarely appears as significant if one examines correlations with the prevalence or progression of silent coronary atherosclerosis or coronary event-free survival, or when one takes into account the very small absolute benefits seen in true primary prevention statin intervention trials when the endpoint is fatal or non-fatal heart attack?

LDL is universally regarded as the "bad" cholesterol. If it is so bad, why is it consistently absent as a factor in studies of the risk of prevalence and progression of silent atherosclerosis? One aim of primary prevention must be to impact prevalence and progression of atherosclerosis. Also, statins are ineffective in this context for both non-diabetics and diabetics.[10,29-32] Why does low or very low LDL characterize half of hospital admissions for heart attack? Then there are all the non-statin drugs, and especially ezetimibe, that lower LDL but do not reduce the event risk even in the secondary prevention setting [33]. Why if LDL is so bad, are the numbers needed to treat so high in true primary prevention? If the NNT found in intervention studies is 50 or 100, or even 25, what about the 49, 99 or 24 who were treated but did not benefit from LDL lowering? Why is cholesterol in general and LDL in particular not associated with the risk of sudden cardiac death, even though it accounts for about 50% of DHD mortality? Also, the focus on relative rather than absolute risk reduction has resulted in widespread inflated perceptions of benefit, confused the risk/benefit analysis, and produced a false sense of security among the millions of statin users. The extensive use of relative risk in this field has been the subject of severe criticism for at least two decades.

INTENSIVE THERAPY FOR DIABETICS DETECTED BY SCREENING

Those who favour widespread screening for type 2 diabetes must offer evidence that there is benefit associated with triggered treatment. A recent study (ADDITION-Europe) looked for this evidence in a multi-country cohort of screen-detected diabetes cases.[34] They were randomized to routine care or intensive care, the latter involving lifestyle advice and targets for blood pressure, total cholesterol and the average blood sugar levels represented by glycated hemoglobin (HbA1c). Approximately 3000 patients from 161 practices in Denmark and England were available for randomization. The intensive treatment targets for HbA1c, blood pressure, and total cholesterol with and without ischemic heart disease were 7%, ≤ 135/85 mm Hg, < 194 mg/dL (5 mmol/L), and < 174 mg/dL (4.5 mm/L), respectively. Most of these newly diagnosed diabetics did not have a history of heart attack or stroke. Aspirin was recommended for all hypertensives. Both the paper and the associated website for the study are silent on the dietary intervention details. In the drive to achieve targets, statins, ACE inhibitors, diuretics, calcium channel blockers and various glucose control drugs such as metformin were used. The primary endpoint was a composite of first cardiovascular event including mortality, morbidity (non-fatal heart attack or stroke) revascularization (coronary artery bypass or angioplasty) and non-traumatic amputation.

After a mean follow-up of 5 years, in the intensive group compared to the routine care group, improvements in cardiovascular risk factors were very small as was the non-significant reduction in the incidence of cardiovascular events and death. The composite endpoints also did not differ significantly between the two groups.

There are several ways of looking at the results. One views the small benefits, while insignificant or close to it, as good news and reason for encouraging screening and early intensive treatment with an arsenal of drugs. Every little bit helps. The other views these as negative results suggesting that the routine and intensive approaches were not that different in practice, and routine practice became by itself more intensive as the study progressed, and that the study itself is not that significant. If the comparison had been

between the intensive treated group and a totally untreated, ignored group, this would probably have produced more impressive results, but such studies, while potentially very informative, are not viewed as ethical. The most pessimistic view calls for both finding and employing more effective approaches to the management of diabetes. This last point relates to the above discussion regarding the very weak evidence supporting statin use in individuals without CVD/CHD. Also, it is highly unlikely that the dietary advice used in this study involved severe carbohydrate restriction, no doubt because it is not realistic in a large population. But for the individual newly diagnosed with type 2 diabetes who is strongly motivated to reversing this disorder or at least halting its progression, this is an option that minimized drug intervention until proven necessary.[35]

SMOKING AND CORONARY HEART DISEASE RISK. MEN VS. WOMEN

A large meta-analysis (study of studies) concerning the difference in coronary heart disease between men and women has just appeared.[36] In this study a total of 86 prospective follow-up trials were included and the final 76 cohorts involved 2.4 million participants. Trials were excluded if they predominantly enrolled individuals with an underlying pathological disorder including type 1 or 2 diabetes, previous cardiovascular disease, kidney dysfunction or cancer. The analysis compared sex specific relative risk for fatal or non-fatal coronary heart disease events in current smokers vs. non-smokers. It was found women who smoked had a 25% greater risk for acute fatal and non-fatal coronary events, a result which was highly statistically significant and unchanged after adjustment for potential publication bias. The relative risk increased by 2% for every additional year of study follow-up, i.e. smoking.

An editorial in the same issue of *Lancet*[37] attempted to put this study in perspective. Heart disease is the main cause of death in the UK, USA and many other developed countries. While there are a number of varieties of heart disease, the World Health Organization lists ischemic heart disease as the leading cause of death worldwide.

The elevated risk found in women is worrisome because more men than women are giving up smoking, and in some societies the number of female smokers is rising. The editorialists also point out that smoking cessation rapidly decreases the risk of death from cardiovascular disease. This is interesting because coronary heart disease has two phases, atherosclerosis with its ever increasing coronary plaque burden, and acute events involving the rupture of vulnerable plaque and the resultant artery blockage. The impact of current smoking on both have been studied and found to be an important factor. Coronary plaque burden as estimated by coronary calcium increases dramatically from never smokers to former smokers to present smokers, and for each group, age also dramatically increases the burden, but women have significantly lower burden (calcium score) in all the above categories of smoking and age (about 5 times higher in men).[38] Rapid cessation of smoking almost certainly has no impact on plaque burden, and thus must remove triggers for plaque rupture, although smoking clearly is significantly involved in setting the stage. However, cessation slows down the accumulation but one is left with the smoking enhanced accumulation and the associated premature increase in coronary artery age. Thus while women in general have a considerably lower risk of heart disease, smoking can narrow the gap.

RED MEAT AND RISK OF TYPE 2 DIABETES IN MEN AND WOMEN

Harvard researchers have just reported on an analysis of accumulated data from the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Studies I and II (NHS I and II)

the latter involving younger women. A total of about 37,000 men and about 167,000 women were involved.[39] For men the follow-up was 20 years and for women 28. One of the strengths of these studies was the repeated updating of information on diet and lifestyle. The incidence of type 2 diabetes was examined for processed, unprocessed and total red meat according to daily intake. One serving of unprocessed meat equalled 85 g (3 oz) of pork, beef or lamb, and one serving of processed meat equalled 28 g bacon or 45 g of hot dogs, sausage, salami, bologna or other processed red meats.

The risk of diabetes showed a consistent increase with intake of red meat in both men and women. Analysis of the HPFS data with a fully adjusted model found that a significant risk appeared for red meat only at high consumption (quartile 5, mean intake 1.44 serving/day). For NHS II the same pattern emerged with significant risk associated with 1.29 servings per day, the mean for quartile 5 but for NHS I increased risk was apparent at an intake of 0.61 servings/day (quartile 2). For processed meat, both in HPFS and NHS I the risk appeared in quartile 2 and increased with increased intake. However, in NHS II, risk of processed meat consumption appeared only at the highest quartile (mean consumption 0.49 servings/day. When the results were pooled, a one serving/day increase in unprocessed, processed or total meat consumption increased the relative risk by 12%, 32% and 14% respectively. The authors also conducted a meta analysis combining this study with earlier ones. For 100 g of unprocessed red meat per day, the increased risk was 19% whereas for processed meant it was 51%.

One interesting aspect of the study was an analysis of the outcome for substituting one daily serving of red or processed meat with on serving of a wide variety of alternative food items such as nuts, low-fat diary products, whole grains, fish and poultry. In all, the examined 15 substitutions and in all cases found significant risk reductions associated with substitution when the reference was meat intake. The results are too extensive to discuss in detail, but in comparison with red meat, substituting one serving of whole grains per day reduced the risk by 23%, nuts by 21%, low fat dairy by 17%, poultry by 10% and fish by 10%

In a news release from Harvard, Professor Frank Hu, who was involved with the study, commented:

"*Clearly, the results from this study have a huge public health implication given the rising type 2 diabetes epidemic and increasing consumption of red meats worldwide. The good news's is that such troubling risk factors can be offset by swapping red meat for a healthier protein"*

CHOCOLATE CONSUMPTION AND CARDIOMETABOLIC DISORDERS

Readers of this Newsletter will be aware that periodically there is news about chocolate and health and in seems to always be good. This is consistent with the evidence based view that chocolate consumption has a positive influence on health, with antioxidant, antihypertensive, anti-inflammatory, anti-atherogenic and anti-thrombotic effects. Chocolate favourably impacts risk factors such as blood pressure, cholesterol levels, atherosclerosis and insulin resistance. A wonder drug with blockbuster financial potential if it could be patented! A recent study has examined the effect of chocolate on so-called hard cardiovascular outcomes such as heart attack and stroke by conducting a systematic review and meta-analysis. The results were presented recently at the European Society of Cardiology Congress and simultaneously published online in the *British Medical Journal*.[40]

Of the seven studies that qualified for inclusion, five reported a significant inverse association (risk reductions-RR) between chocolate intake and cardiometabolic disorders. Comparisons were based on the lowest vs. the highest levels of consumption but the studies differed in the presentation of intake. For example, typical results were

reported for risk reduction (RR) of coronary heart disease (57%), cardiovascular disease mortality 50%, and incident diabetes 35%, but only in men. The overall pooled results (meta-analysis) found a 37% reduced risk for any cardiovascular disease and 29% for stroke. The beneficial effects were attributed to the high polyphenols content of cocoa products which probably result from increasing bioavailability of nitric oxide with related improvements in endothelial function, reductions in platelet function, additional beneficial effects on blood pressure, insulin resistance and blood lipids. Benefits are seen even without daily consumption, and when stratified by quartiles, the mean intake typically ranged from 1.7 to 7.5 g/day. One-eighth of a 100 g bar is about 12 grams which for dark chocolate is about 30 calories.

BIG PHARMA. THE COST OF DOING BUSINESS

According to a tabulation in the book *Childhood Under Siege. How big business targets children,* by Joel Bakan (Alan Land Canada—Penguin Group, 2011), in the 13 years between 1997 and 2010, pharmaceutical companies paid out a total of $6.77 billion in settling claims of wrongdoing and paying criminal and civil fines. The list does not include the fine paid by Johnson & Johnson of 258 million over Risperdal marketing tactics, the 2.3 billion criminal fine paid in late 2009 by Pfizer in a case involving off-label promotion of Bextra and three other drugs, nor the 520 million settlement paid by AstraZeneca over off-label marketing of Seroquel. It is significant that these fines generally represent a small percentage of the lifetime earnings of the drugs in question. In the U.S., the big stick the government has is to deny reimbursement for a company's products by the publicly supported health care system. Your editor does not recall this ever being used. Bakan's book incidentally, is highly recommended.

Some perspective regarding the magnitude of these fines is available from the following data.

WORLDWIDE DRUG SALES 2010
TOP 15 PRESCRIPTION DRUGS
(Source: Bloomberg, Feb 10, 2011)

DRUG	$(BILLIONS-US)	INDICATION
Lipitor	10.7	Cholesterol lowering
Plavix	9.43	Blood clot prevention
Remicade	7.99	Psoriasis, arthritis, Crohn's disease
Advair	7.94	Asthma and COPD
Enbrel	7.23	Rheumatoid Arthritis
Abilify	6.78	Antipsychotic and antidepressant
Humira	6.55	Rheumatoid arthritis
Avastin	6.22	Colorectal cancer
Rituxan	6.11	Lymphoma
Diovan	6.05	Hypertension
Crestor	5.69	Cholesterol lowering
Seroquel	5.30	Schizophrenia and bipolar disorder
Herceptin	5.22	Breast cancer
Zyprexa	5.03	Bipolar mental disorder
Singulair	4.99	Asthma

Just these 15 drugs total about $100 billion sales. The Top 500 prescription drugs had 2010 worldwide sales of about $500 billion. Prescription drugs brought in over $300 billion in the U.S. Lipitor has now held the No. 1 ranking for 9 straight years. Crestor had the biggest yearly gain (2009-2010) of 26%. Typical yearly gains were in the 5-6% range.

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RESEARCH REPORT

BOTOX FOR THE BRAIN
THE BRAVE NEW WORLD OF NEUROENHANCERS

by William R. Ware, PhD

"Advances in cognitive neuroscience make cosmetic neurology in some form inevitable and will give rise to extremely difficult ethical issues." A. Chatterjee, MD, Department of Neurology, University of Pennsylvania.

INTRODUCTION--THE SLIPPERY SLOPE

As used in psychiatry and neurology, the term neuroenhancer refers to a drug, generally a prescription drug, which improves mental performance and focus and is believed to enable the user to work effectively over longer hours. They are also called smart drugs. The classical example is caffeine which has been used as a neuroenhancer for eons, and aside from tea and coffee, it is now available in high concentrations in a variety of soft drinks and can be acquired in a more or less pure form in over-the-counter preparations designed for those who wish to or need to stay awake. Some call the prescription of neuroenhancers *cosmetic neurology or cosmetic psychiatry,* but while the issues that arise in the field of cosmetic surgery or Botox injections are completely different, there can be no doubt that an alarming trend is underway.

The current debate in the psychiatry and neurology community concerns the ethical aspects of writing prescriptions where the only indication is the desire for neuroenhancement. The prescriptions are currently off-label, i.e. the drug is not approved by regulatory bodies for the indication in question. The motivations exhibited by these "patients" range from the desire or need to perform better in school or exams, achieve admission to a top school, or achieve better performance in important tasks encountered in the workplace and thus increase the chances of promotion and decrease the chances of being fired. School children can easily fake attention deficit/hyperactivity and get the desired stimulant prescription, or they simply acquire the pills from friends or off the street. Parents may confront doctors with the demands for enhancers for their children because they are concerned about the competitive school environment with success defined as high SAT scores and admission to universities or colleges in the top tier. The drugs may then be needed to do well in the highly competitive atmosphere of these top centers of higher education, especially if the goal is then admission to professional or graduate programs, again at top institutions. Parents can argue that the drugs are necessary for otherwise their children are at what they view as a significant disadvantage when competing with peers who are on enhancers. The social networks that dominate the lives of many young people also stimulate the demand for and use of neuroenhancers. Critics simply take the position that the academic use of neuroenhancers is tantamount to cheating.

In the workplace, employees may find they are competing with coworkers who take enhancers and, unless they do likewise, they place themselves at a perceived disadvantage. This may become critical for someone involved in an important project involving high pressure, the need for high performance and innovation, and in many cases lots of overtime. The extreme scenario is where management pressures employees in some of the critical development, research or production groups to take enhancers in order for the company to compete more effectively. Another area where neuroenhancers are used is in the medical education setting where long (some say excessive) hours on call are required, or jobs where long hours of high pressure is the norm such as in busy emergency departments. In this context, enhancers frequently address, and some say quite successfully, wakefulness and alertness issues. Use can continue after certification is achieved if these individuals are employed in high stress shift work, again for example in the ER setting, or have become dependent on the drug.

Precedent is already set in the military where psychopharmacy is widely and officially practiced for the purpose of improving combat performance. There is evidence that the use of such drugs is widespread. The dangers of addiction, which will be discussed below, most certainly arises here as well in non-military settings. This is the so-called slippery slope which spirals out of control until vast numbers of individuals from school children to engineers, scientists, physicians, geeks and CEOs are operating at a level partly determined by neuroenhancers and some develop addiction.

A curious inconsistency in the notion held by some professionals and many laypersons that the neuroenhancers are just fine is the generally held opinion that in athletics, performance enhancers are wrong and justifiably outlawed. One of the greatest pitchers in baseball is currently being tried for lying under oath regarding the use of performance enhancers. A doctor has just entered a guilty plea regarding US/Canada cross-border trafficking in performance enhancing drugs and could face jail time. Sports fans pay to see the results of training and talent, not who has the greatest success with performance enhancement. Others argue performance enhancement makes a mockery of recording athletic achievements, idolizing record holders, and even the whole notion of halls of fame. Those who attempt to reconcile these two views point out that professional athletic performance influences outcomes which are the basis of gambling, and thus regard performance enhancing as equivalent to outcome fixing. The argument for non-professional athletes is considerably murkier. Fans pay to attend events and performance enhancing drugs bias outcomes that are of great importance to the athletes' future, turning professional, and acquiring income from endorsements and exhibition performances. It is interesting that even the drug modafinil, widely used in cognitive enhancement and to promote wakefulness, is banned in athletic competition and at least one athlete has been penalized after testing positive for this drug.

There are those in the medical and academic communities who view these drugs as benign and in fact wonder drugs that are just the answer to problems common in the modern world. They are a symbol of remarkable scientific progress and innovation. There are also those who hold a quite different opinion, i.e. that these drugs are dangerous, addictive, function by mechanisms that are only partially understood, if at all, and the risk inherent in their long-term use has never been critically examined. In addition, there appears to be a large variation in the incidence of adverse side effects, but when they occur, they are serious and dangerous. Thus the debate centers around both the ethical questions and the problem of serious and potentially life-altering side effects already observed and documented in some, but not all users of the type of drugs being promoted for neuroenhancement.

The issues seem clear.

- There are no significant long-term (> than a year) studies concerning the safety of neuroenhancers or in fact for most drugs used in psychiatry.
- Will higher and higher doses be needed to maintain the desired level of enhancement?
- Do these drugs induce permanent brain changes, as some critics assert, and are these changes detrimental?
- Many neuroenhancing drugs currently used off-label or purchased on the street have long and alarming lists of short-term side effects.
- Neuroenhancement can provide very selective benefits while simultaneously inducing complementary deficits in intellectual and social performance.
- Anecdotal evidence, mainly from case histories, suggest that some drugs currently used for neuroenhancement can is some cases lead to depression and psychosis and take one down the path of polypharmacy which ends up in disability and in some cases institutionalization and suicide.
- Is a society where neuroenhancement is the norm a society we really want? Is it a society that is better than what we have now? Or should we simply stick to coffee, tea and supercharged soft drinks, and if this is not enough, visit the No-Doz® section of the drugstore?
- Are the elderly a special case where impaired memory or evidence of cognitive impairment may be an indication for drugs used for neuroenhancement?

- Neuroenhancement involves giving drugs to healthy, normal individuals in an attempt to make them better and smarter, not to sick people to deal with their illness. It is unlikely that insurance will cover this use and there will no doubt be obstacles to regulatory approval for this use. As an approach to dealing with competition, this may give an advantage to the rich and educated.

This review is being presented because of the belief that society is shortly going to be forced to confront the issues raised above, that regulatory agencies are going to be under pressure to approve drugs for enhancement purposes, and that for the pharmaceutical industry this is an opportunity to greatly expand the market for psychiatric drugs. Societies in developed countries are already starting to face decisions regarding neuroenhancement. Therefore it becomes very important to understand the potential dangers, especially of existing drugs. Many of the same issues will arise as new drugs designed purely for neuroenhancement come up for approval. They are apparently in the so-called pipeline. This is a hot topic in psychiatry and neurology and medical ethics with a quite considerable literature already in place. A good informal discussion, mainly in the university-college context, can be found in *The New* Yorker.[1]

THE DRUGS

If one believes that the central issue is risk vs. benefit rather than philosophical and ethical, then it is necessary to examine the drugs in current use. Unfortunately, the list is long and studies on use prevalence in various populations are very limited. The major performance enhancing drugs currently in use off-label or illegally include modafinil (Provigil), methylphenidate (Ritalin) and a combination of amphetamines (Adderall). The street name for amphetamines including Ritalin is “Speed.” Ritalin and other amphetamines are used extensively to treat attention deficit/hyperactivity disorder (ADHD) in both children and adults. Modafinil, which not only goes by the name Provigil but several others, is an analeptic drug approved in the US for treatment of narcolepsy, shift-work sleep disorders and excessive daytime sleepiness associated with sleep apnea. Thus it appears to address the problem of staying awake but also operates to some extent as a smart drug. Modafinil appears to operate via a number of complex mechanisms.[2] Other drugs include 2-oxo-1-pyrrolidine acetamind (Piracetam, a GABA derivative), anti-dementia drugs (acetylcholinesterase inhibitors donepezil, galantamine, rivastigmine) and the glutamate receptor blocker memantine. This non-stimulant group presumably joined the neuroenhancer family for use by well individuals because of evidence of inducing improvements in patients who were cognitively impaired. However, these cognitive enhancers mainly improve performance, primarily or exclusively, in individuals with significant impairment.[2,3] This list is probably not complete but indicates the problems with risk-benefit analysis since we are dealing with a number of drug classes.

If these drugs are really benign, then one of the strongest arguments against neuroenhancement disappears. Short term studies of adverse side effect of stimulants are limited and long-term studies virtually non-existent. Furthermore, for many of the drugs in use, only a few very small, short-term studies, if any at all, have been carried out on healthy, normal individuals and the important questions regarding long-term harm and serious adverse effects have never been systematically studied. As regards stimulants used for ADHD, studies do not differentiate between those who really do not have ADHD and those that do when studying an ADHD cohort for side effects, since overdiagnosis and overtreatment is in general ignored or denied. Some hold the view that ADHD is seriously over diagnosed and over-treated, which gives added importance to adverse side effects. Nor are there any studies of adverse side effects for those who manage to get drugs such as Ritalin from friends or off the street and use them for recreational or enhancement purposes. Finally individuals taking stimulants or other psychiatric drugs often quickly stop taking them because they cannot tolerate the side effects. These cases do not generally enter into the databases for side effects.

Finally, there is the issue of the impact of any of these drugs on brain development and brain changes, which extend from conception to roughly the end of the teenage period. The design of such studies would constitute a profound challenge, and financing such studies would require deep pockets indeed. The large number of drugs that are eligible for study underscores the general conclusion that the required risk information will never be acquired. One can fall back on generalities. The complex biochemistry, pathways, receptors, networks, etc. in the brain are only partially

understood. Furthermore, the mind-brain connection is not understood at a level where the information is useful. The general consensus among those who do not have an agenda is that the mechanisms of mental disorders are poorly understood, if at all. Thus one can conclude on general principles that it is not a good idea to mess around with the brain by introducing chemicals never before encountered. While the justification that someone is really acutely sick and needs treatment of course has merit, neuroenhancement is a different matter entirely which is at the other end of the spectrum and involves mentally and physically healthy individuals where the goal is to make them smarter, brighter, more focused, more able to engage in sustained intellectual efforts, stay awake and able to compete more effectively and successfully in the modern world. The obvious question then becomes, are unknown long-term risks of neuroenhancers, some potentially involving permanent brain alteration, worth taking for the perceived benefits some derive?

Women of childbearing age present a special situation. Psychiatric drugs use, especially during the first trimester, can have profound effects on fetal development and the risk of permanent abnormalities.[4,5] But the lag time between conception and awareness of being pregnant, as well as the wash-out time for some drugs can put the fetus at risk for a period well into the first trimester, and the first month has been shown in many studies be especially critical in the context of adverse effects. Recall that this argument is used successfully to justify the suggestion that all women of childbearing age take folic acid and governments even mandate fortification of foods with this in mind. There are also serious issues with withdrawal from psychiatric drugs when pregnancy is confirmed since the process must be tapered over a period of time or very serious effects are likely.

Some insight into risk can be obtained by examining what is known about the side effects of stimulants since this class has a long history of use in both children and adults and there is considerable information available, especially regarding Ritalin, Concerta and Focalin and the amphetamine mixture called Adderall. Note that these are all classed in the US as so-called Schedule II drugs. The nature of the list can be discerned by the company they keep, which includes cocaine, opium, morphine, codeine, methadone, oxycodone, and hydromorphone! Addicts “snort” stimulant drugs just as they snort other Schedule II drugs in the process of achieving a high. Drugs are on this list because they have the potential for leading to severe psychological or physical dependence and abuse. Thus high on the list of adverse side effects for stimulants is the risk of addiction, independent of whether they are used for AHDH or as neuroenhancers. Parents should be made aware of this.

Other adverse mental effects reported in clinical trials of stimulants include drowsiness, loss of alertness, convulsions, dopey behavior, depression, agitation, restlessness, and irritability. Rates range from 5% to about 40% depending on the effect.[6] FDA post-marketing adverse event reports concerning methylphenidate products such as Ritalin and Concerta include suicidal ideation, aggression and violent behavior. A March 2006 FDA report indicated that every type of stimulant drug potentially could cause psychosis or mania, particularly hallucinations at the usual doses employed to treat ADHD, and these results included confirmation by rechallenge (administration for a second time caused recurrent psychosis).[6] Another side effect is termed being “hung up” which translates roughly into compulsive behavior including over focusing and repetitive behavior. Of course, if these side effects occurred in the majority of users, the drugs would no longer be on the market.

In his recent (second edition) medical textbook *Brain Disabling Treatments in Psychiatry*, Dr. Peter Breggin points out that experts generally agree that Ritalin affects normal children in the same way as those diagnosed with ADHD. Breggin lists and documents a number of stimulant effects commonly misidentified as therapeutic or beneficial which include obsessive-compulsive behavior, social withdrawal effects, and behaviourally suppressed effects. He also discusses at length brain damage and dysfunction caused by stimulants including atrophy, gross brain dysfunction, abnormalities in brain chemistry and microscopic pathological changes. One serious problem he emphasizes throughout the book is that the drugs also impair an individual’s ability to detect adverse effects but rather confuse them with benefit. He terms this “spellbinding” although it has a fancy medical name as well.[6] Spellbinding presents a serious obstacle to those trying enhancers to see if they work and if there are adverse effects. Since the drugs being used have never undergone long-term testing with normal, healthy cohorts with the object of uncovering adverse effects which include brain disabling

and spellbinding, and since those trying these drugs for neuroenhancement may never be able to detect subtle and perhaps permanent damage, it is hard to emphasize strongly enough that real and very complex risks are indeed involved. They are also risks easily dismissed by advocates of neuroenhancement, especially those who only believe in the most compelling evidence-based arguments. After all, these risks are routinely dismissed or downplayed when the drugs are used for therapy, a fact of life which complicates decision making for the layperson desirous of valid and complete information concerning risks, but generates books full of case histories which can be profoundly alarming.[7-9] The information really needed is either not available, nonexistent or ignored. Part of the driving force behind this situation, including denial and suppression, is simply that benefits are emphasized for the sake of profits, and the profits are huge by any standard.

If one is doing a risk/benefit analysis, it would seem that little more needs to be said. For a normal individual with no real mental illness to attempt neuroenhancement with stimulant drugs does not appear to be a good idea. Thus the enhanced ability to focus and settle down to a task, which some equate to being smarter or better able to function at certain tasks, comes at a high price of risk of known side effects. Long-term risks that would apply to continuous use over a number of years of stimulant uses to reach a permanent higher-level performance have never been studied. However, in groups where continuous use has occurred, there is obviously a selection process since those who experience some adverse effects will simply stop taking the drug. At the other extreme, addiction will occur, perhaps along with psychosis, which will then lead to additional medication. This is an all too common scenario.

With respect to the other classes of drug used off-label for neuroenhancement, side effect information is variable. The following include examples of three different classes of drug also used off-label for neuroenhancement. More details can be found in the *Physicians Desk Reference* and drug company and other websites.

Modafinil (Provigil). From the drug label information:
Serious rash requiring hospitalization has been reported in adults and children and the drug is not approved for use in pediatric patients (<16) for any indication. Other commonly observed side effects include headache, nausea, both frequently observed, and nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness and indigestion, all much less frequently observed. Psychiatric adverse experiences include mania, delusions, hallucinations, suicidal ideation, some resulting in hospitalization.

Memantine. Common adverse reactions observed include confusion, dizziness, drowsiness, headache, insomnia, agitation and hallucinations.

Donepezil (Aricept). Nausea, vomiting, diarrhea, loss of appetite, dizziness, drowsiness, weakness, trouble sleeping, shakiness and muscle cramps.

This information must be interpreted with caution. Treatment was on-label and thus for conditions that were indications for treatment, rather than for well individuals. Also, one can conclude from the evidence uncovered in court cases that side effects may be significantly and intentionally understated or suppressed in industry supported trials.

THE ETHICAL DILEMMA

At present, neuroenhancers are prescription drugs or illegal street drugs and thus the physician asked for a neuroenhancer prescription has a problem since a drug is being given off-label, not to treat any disorder, but purely for anticipated enhancement of performance or to gain a competitive advantage. Couple this with the lack of information in general regarding long-term adverse effects on patients of all ages, and one can easily appreciate that for most doctors, there will probably be (or should be) a fairly high level of discomfort. Remember the oath that emphasized “first do no harm.” Exactly the same situation occurs with sport performance enhancers. Those seeking neuroenhancer prescriptions may solve this problem by faking the appropriated disorder, e.g. ADHD or a sleeping or wakefulness problem, and in come cases this will work. Students do it all the time. If the past is any

guide, there will always be physicians willing to play along with the request for such off-label prescriptions, and how this will be treated in terms of legality or professional misconduct remains to be seen. The whole ethical issue is now the subject of ongoing debate and there is a large relevant literature.

The growing use of neuroenhancers has prompted the formation of the Neuroethics Society (www.neuroethicssociety.org) representing a subfield of bioethics. Its mission is to address the ethical aspects of developments in neuroscience and neuropsychiatry. There is no doubt that the current activity in the field of cognitive enhancement, and especially the research on new drugs targeted at healthy individuals, will challenge this organization. Another challenge will be to determine if the organization is biased by industry ties.

The two sides to the ethical issue are clearly seen in the recent literature. In a commentary in *Nature* Henry Greely from Stanford Law School was joined by other academics from various medical science disciplines to argue that society must respond to the growing demand for cognitive enhancement.[10] We are told that "We should welcome new methods of improving our brain function." They present a comprehensive agenda addressing issues such as fairness and socioeconomic disparities inherent in cognitive enhancement, research into effectiveness of drugs in healthy individuals, full dissemination of information on risks, benefits and alternatives, and legislative action to protect the effort and use. A tacit assumption appears to be that benefit far outweighs risk ands that long-term risk can and will be determined. The article is illustrated with a picture of some Adderall pills. A similar position is advanced by Steven Hyman from Harvard.[11] In dealing with the risks of stimulant drugs he argues that these drugs have been used for decades and long-term cohorts have been followed for a variety of reasons, "making it unlikely that we are missing some truly awful long-term side effect." He should read what Peter Breggin has to say in two chapters on stimulants and check out the references![6] But Hyman does admit to the absence of "solid empirical knowledge" regarding risks.

Sahakian and Morein-Zamir from the University of Cambridge have recently provided a good discussion of what they call the "rights" and "wrongs" of the use of cognitive enhancers in healthy adults.[2] They discuss many of the observations detailed above concerning alleged or real benefits in healthy individuals and describe a survey of academics who took modafinil. Those who used this drug spoke highly of the experience with global effects on attention, working memory, word finding, improved sustained hard thinking and increased mental energy. The authors also cite applications in the military and even for surgeons. College students report similar levels of satisfaction.[1]

Sahakian and Morein-Zamir also provide a lengthy discussion of concerns. Some of these have been mentioned above. They included the absence of long-term studies, the potential dangers to the developing brains of children and teenagers, inequalities and fairness associated with access to these drugs, unfair advantages in many settings, and that some aspects of the development of a successful and intelligent work ethic could be replaced by taking a pill. Also, they point out that intelligence is complex and no one knows what these drugs do in general and advocates are simply looking at certain manifestations which can be manipulated. They quote Anjan Chatteerjee from the University of Pennsylvania as saying that "No one has conducted thorough studies about how brain-boosting drugs would affect healthy people after weeks or months (how about years?) of use." Finally, they discuss surveys that indicate that a significant fraction of some populations (e.g. students and parents) held a favourable view of the underlying philosophy of using cognitive enhancing drugs.

Along with all of these calls, both radical and conservative, for increased use or consideration of cognitive enhancers, the one thing ignored is the almost complete impossibility of demonstrating long-term safety in large controlled studies. Will university ethics committees approve giving powerful drugs with documented side effects to healthy individuals? True, healthy individuals can no doubt be paid to participate, but those who experience early side effects would no doubt drop out, and compliance over say several years is hard to imagine. Proponents look forward to targeted drugs for cognitive enhancement in healthy individuals that have been proven safe. But arguments have been presented repeatedly in the above discussion and in the literature that proof of low or no risk is near impossible, and in fact simply fantasy, just like the Brave New World.

CONCLUSIONS

Neuroenhancement and cosmetic neurology are completely consistent with the modern philosophy that there is a pill for almost everything and if you have a problem, Big Pharma is always there to offer a helping hand. In the academic setting, if you want an advantage, or in fact avoid being disadvantaged, enhance your intellectual powers and your ability to focus, or if it is desired to combine an active and time consuming social life with the need to do some studying and writing, then talk to your buddies down the hall or find someone who sells enhancers. Parents take note of what may be necessary to get your kid in an Ivy League school. If you are an ER doctor and have trouble working at 100% for the whole shift or a professor desperate to achieve tenure, follow the example of some of your peers and take modafinil. It is said to be a wonder drug.

Twenty or thirty years ago the above paragraph would be considered somewhat absurd. Those who view it as a valid description of the present, and an indication of the future can feel secure in that the negative arguments are doomed to never get off the ground because of the near impossibility of doing studies which will define the real long-term risks. It is interesting that serious, concerned people are suggesting that urine samples should be required before students take important exams such as SATs.

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