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PHYSICAL ACTIVITY IN YOUNG CHILDREN

PHYSICAL ACTIVITY AND OBESITY

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“WAKEFULNESS ENHANCER” ROUSES CONCERN

SHOPPING ‘TIL WE DROP—WHAT IS WRONG WITH IT?

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HIGHLIGHTS AND EDITORIAL COMMENTS

1-1 TOTAL ENERGY EXPENDITURE AND PHYSICAL ACTIVITY IN YOUNG SCOTTISH CHILDREN

The epidemic of childhood obesity has been attributed largely to a decline in total energy expenditure (**TEE**). This study postulated that the lifestyle of contemporary young children is sedentary.

Levels of TEE were low at ages 3 and 5 in both sexes. Lifestyles in this sample of youngsters were sedentary. This would increase risk of obesity. Their total energy expenditure was significantly lower than the UK estimate average requirement for energy for children.

Children typically spent only 20-25 min per day in moderate to vigorous physical activity. Present recommendations are that they should accumulate at least 60 min daily. “There is a widespread perception among parents and health and educational professionals that young children are spontaneously active. Actually, modern children establish a sedentary lifestyle at an early age.”

Prevalence of childhood obesity has increased strikingly in recent years.

1-2 PHYSICAL ACTIVITY AND OBESITY

The nature of human physiology is such that it is extremely difficult, if not impossible, to maintain a healthy bodyweight with a low level of physical activity.

Obesity arises from an imbalance in which energy intake exceeds energy expenditure. This means that sedentary people must maintain a low intake of energy to avoid obesity. Human physiology did not develop to support restriction of energy intake. It is difficult for most people to do so consistently over time

We have to teach children (and adults) to use their intellect to push back against the environment. Such a change can be done by eating a little less and being a little more physically active than ordinarily. Small changes would counter the natural tendency to succumb to the environment.

“We suggest that weight gain in 90% of the US adult population could be prevented by reducing positive energy balance by only 100 kcal per day.” Small and achievable changes in behavior can have a big impact.

1-3 “ME TOO” PRODUCTS—FRIEND OR FOE?

Me-too products create competition among drug and device manufacturers. Competition is a powerful driver for better quality and lower costs. Health care leaders who struggle to provide good care with limited resources see me-too products not as a problem, but as an important part of the solution.

The first product in a new class defines the baseline value equation. [Value = benefit / harm-cost] The manufacturer may set a high price and may have no trouble selling the product at its asking price. When a second product in the same class comes along, its manufacturers must offer a better value. That product must lead to a better outcome or it must be less expensive.

For market forces to really work, physicians have to choose products as if costs matter.

1-4 WHY PEOPLE SMOKE

“If it were not for the nicotine in tobacco, people would be little more inclined to smoke than they are to blow bubbles.”

Experimenting with smoking usually begins in the early teenage years. It is driven predominantly by psychosocial motives. Smoking a cigarette is a symbolic act of rebellion, and a statement of independence. The desired image is sufficient for the novice smoker to tolerate the aversion of the first few cigarettes, after which the pharmacological factors assume much greater importance. As the force from the psychological symbolism subsides, the pharmacological effect takes over to sustain the habit. Absorption of nicotine from the lung and transfer to the brain is almost instantaneous and complete.

Tolerance soon develops, and chronic users probably do not obtain absolute improvements in performance, cognitive processing, or mood. A plausible explanation for why smokers perceive cigarettes to be calming may come from a consideration of the effects of nicotine withdrawal. Smokers start to experience impairment of mood and performance within hours of their last cigarette, and certainly overnight. These effects are completely alleviated by smoking a cigarette.

“Early cessation is especially important.”

1-5 OMEGA 3 FATTY ACIDS AND CARDIOVASCULAR DISEASE—Fishing For A Natural Treatment

Omega 3 fatty acids (**O3FA**) from fish and fish oils can protect against coronary heart disease (**CHD**). In this era of polypharmacy, many persons believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits.

The American Heart Association recommends:

Patients *without* documented CHD should eat a variety of fish (preferably oily) at least twice weekly. Diet should also include vegetable oils.

Patients *with* documented CHD should consume 1 g of O3FA and O6FA daily.

Physicians may prescribe 2-4 g/d of O3FA and O6FA daily, provided as capsules, for patients with hypertriglyceridemia.

1-6 MEMANTINE TREATMENT IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER DISEASE ALREADY RECEIVING DONEPEZIL

In October 2003, the FDA approved memantine (*Namenda*) for treatment of moderate to severe AD. Memantine is a blocker of the receptor for aspartate. It is a new class of drug.

This study hypothesized that adding memantine (*Namenda*) to donepezil (*Aricept*) would result in clinical benefit and would be well tolerated.

Memantine resulted in significant statistical, but only slight clinical benefit when added to donepezil. It appeared safe.

Investigators, as in this report, often stress statistically significant improvement, not clinical improvement. This may be misleading. In my view, the outcome of this study is disappointing.. The investigators place a spin on benefits by noting the statistically significant outcomes. This may appear to be an impressive result, but it is not clinically important.

1-7 RISKS OF TESTOSTERONE-REPLACEMENT THERAPY AND RECOMMENDATIONS FOR MONITORING.

Hypogonadism is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms: diminished libido and sense of vitality, erectile dysfunction, , depression, anemia, and reduced muscle mass and bone density. Prescriptions for testosterone supplementation have increased substantially over the past decade.

Reports indicate that testosterone replacement may produce a wide range of benefits: improvement in libido, bone density, muscle mass, body composition, mood, erythropoiesis, and cognition.

No studies have yet been initiated to assess benefits and risks, especially possible stimulation of prostate cancer. But, “Despite decades of research, there is no compelling evidence that testosterone has a causative role in prostate cancer”.

There is no compelling evidence to suggest that men with higher testosterone levels are at greater risk of PC or that treating men with hypogonadism with exogenous androgens increases risk. Nevertheless, the authors advocate routine biopsy in all men presenting for replacement therapy

Should primary care clinicians deal with this problem? Should they refer patients seeking therapy to a urologist with considerable experience? At the present stage of development, I would follow the second course.

The value of a therapy has been described as:
$$\text{Value} = \frac{\text{benefits}}{\text{harms-costs}}$$

I believe the benefits are somewhat nebulous and unknown long-term. Harms are potentially great. Cost is considerable considering consultation and laboratory fees as well as the cost of the testosterone.

1-8 HYPOGONADISM IN ELDERLY MEN—WHAT TO DO UNTIL THE EVIDENCE COMES

A long-awaited report from the Institute of Medicine (IOM) concluded that there is insufficient evidence that testosterone benefits elderly men.

Many studies document that serum testosterone levels decrease as men age. In contrast to the precipitous and profound decrease in estradiol concentrations in women at the menopause, the decrease in testosterone levels in men occurs moderately and gradually over a period of several decades—from about 600 ng/dL at age 30 to about 400 at age 80. One study reported that about 20% of men over age 60 had total serum testosterone levels below the normal range for young men.

A still unanswered question is whether this decrease is physiologic (perhaps conveying a benefit) or pathologic (causing harm).

Another unanswered question is whether increasing the low-level testosterone in elderly men to the level of younger men will exacerbate testosterone-dependent diseases such as prostate cancer and benign prostatic hyperplasia.

1-9 HELICOBACTER PYLORI ERADICATION TO PREVENT GASTRIC CANCER IN A HIGH-RISK REGION OF CHINA

Over 7 years, in a subgroup of patients *without any precancerous lesions* in the stomach, eradication significantly reduced risk of developing GC.

Other investigators suggest that Hp-infected patients with normal findings on endoscopy are at risk of development of GC. Therefore, in high-risk populations, all patients with *H pylori* infection with no precancerous lesions should consider the use of eradication treatment for gastric cancer prevention.

Further studies are required to determine the role of eradication in those with precancerous lesions.

1-10 FOLIC ACID AND THE PREVENTION OF NEURAL TUBE DEFECTS

A public health policy should include both the mandatory fortification of flour and a recommendation that all women planning a pregnancy take 5 mg a day. Each year about a quarter of a million pregnancies result in the birth of an infant with NTD, or an abortion performed because of such a defect. 85% of them could be prevented if all women took 5-mg daily before pregnancy and during the first trimester.

A high percentage of women of childbearing age have unplanned pregnancies. Since the beginning of pregnancy cannot be predicted in these women, I believe a good case can be made to recommend all women at risk for pregnancy routinely take FA daily. Primary care clinicians should take the opportunity to so advise their younger women patients regardless of the reason for the consultation.

The benefit/harm-cost ratio of FA is high. Although overall risk is low, benefit may be great for individuals. The harm is nil. Cost is low. Considering the devastating effect of NTD for the child and the family, I believe women at risk of pregnancy should be informed and be able to choose if the cost and inconvenience of taking 5-mg daily FA is reasonable. RTJ

1-11 CORONARY ARTERY CALCIUM SCORE COMBINED WITH FRAMINGHAM SCORE FOR RISK PREDICTION IN ASYMPTOMATIC INDIVIDUALS.

In an intermediate-to-high-risk cohort with coronary risk factors, the risk of a non-fatal MI or CHD death in those with a FRS risk score over 20% was 14 times that of those with a FRS of less than 10%.

The CACS significantly modified the risk prediction in all categories of the FRS score of at least 10%, but not when the FRS was less than 10%. When the CRCS was more than 300, the increment in predicted risk was equal to a 3% to 9% increase in the 10-year event risk compared with FRS alone for every category of FRS estimate. The risk of a non-fatal MI or CHD death in those with a CACS over 300 was 4 times that of participants with a CACS of zero.

Would adding CACS determination modify my approach to the patient? I believe it would have no effect. My advice about risk-factor control would remain the same as that predicted by the FRS alone.

Primary care clinicians have a broad base of risk factors to estimate prognosis. We do not yet adequately apply them to individual patients. I do not believe adding another factor will be of any clinical advantage. RTJ

1-12 EFFECTS OF AN AD LIBITUM LOW-FAT, HIGH-CARBOHYDRATE DIET ON BODY WEIGHT, BODY COMPOSITION, AND FAT DISTRIBUTION IN OLDER MEN AND WOMEN.

This is a select abstraction of an interesting article. It describes what might be considered the obverse of the Atkins (high fat, low carbohydrate) diet.

The HCLF diet consisted of 18% fat; 19% protein; and 63% carbohydrate.

Subjects on the HCLF diet consumed about 600 K/cal daily less than those in the liberal control diet.

“Low-fat, high-carbohydrate diets may reduce body weight via reduced food intake, since complex carbohydrate-rich foods are more satiating and less energy dense than higher-fat foods.”

Food choices in the HCLF diet were limited—no sweets and few snacks allowed. I doubt many free-living overweight persons would adhere to the diet for very long.

I consider this an interesting, but not a clinically significant study. It was performed under strict observation. Food was provided by a metabolic kitchen. It lasted only 12 weeks. There were few subjects.

Weight-loss diets have become a multimillion dollar industry. There are many types of diet and approaches to dieting. Gullible overweight persons in the USA seek a quick fix. There is none. None of the diets works consistently over time. Most individuals gradually gain back any weight lost, regardless of the diet.

A calorie is a calorie, is a calorie, is a calorie. RTJ

1-13 THE EFFECTS OF STRONTIUM RANELATE ON THE RISK OF VERTEBRAL FRACTURE IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS

Strontium ranelate is an orally active agent recently re-introduced for treatment of osteoporosis. It consists of two atoms of strontium and an organic moiety. It acts in a dual manner to stimulate formation of new bone and decrease bone resorption.

SR treatment of postmenopausal osteoporosis led to early and sustained reductions in risk of vertebral fractures. In a high-risk group of women with osteoporosis, the NNT to prevent one new vertebral fracture over 3 years = 10

There were no significant differences between groups in the incidence of serious adverse effects. Diarrhea was more common in the SR group (6%). Withdrawals were similar. There was no change in vitamin D metabolites.

“The current trial establishes the efficacy of strontium ranelate, a familiar element relaunched as a new compound, in reducing the risk of vertebral fractures and its role in the armamentarium of therapy for osteoporosis.”

1-14 EFFICACY AND SAFETY OF LOW-DOSE ASPIRIN IN POLYCYTHEMIA VERA

The increase in the red cell mass in PV causes hyperviscosity of the blood, a major determinant of circulatory disturbance. PV is associated with an increase in thromboxane synthesis. This suggests that thromboxane-dependent platelet activation is a major cause of thrombosis.

Thrombotic complications are a major cause of illness and death in untreated patients.

Long-term, low-dose aspirin, used as primary prevention, safely prevents thrombotic complications in patients with PV. NNT to prevent myocardial infarction, stroke, major venous thrombosis, pulmonary embolism, or death from cardiovascular causes over 3 years = 21 to 34.

Major bleeding events associated with low-dose aspirin occurred in one in 26.

PV is the most common of the chronic myeloproliferative disorders. Primary care clinicians will likely refer patients to a hematologist, but may be responsible for long-term follow-up. RTJ

1-15 DAILY ASPIRIN—ONLY HALF THE ANSWER

Thrombosis causes much of the illness and death in patients with polycythemia vera. No part of the vascular system is spared. There is a predilection for peripheral arterioles and cerebral and abdominal vessels. Thrombosis develops in about 40% of patients, most often before or at the time of diagnosis. Rates of fatal thrombosis may be high. Most arterial thrombi occur in small vessels and can cause erythromelalgia and ocular migraine. PV also is a leading cause of hepatic vein thrombosis. Attempts to control erythrocytosis by phlebotomy often fail to diminish the high rate of thrombosis.

Increased blood viscosity is a paramount cause of large-vessel arterial and venous thrombosis. It is in the large vessels that the negative effect of high hematocrit is most pronounced.

An apparently normal hematocrit may *not* be normal in patients with this disease. A safe target is under 45% in men and under 42% in women. Viscosity of the blood rises dramatically at hematocrit levels above 45%.

1-16 POISED TO CHALLENGE NEED FOR SLEEP, “WAKEFULNESS ENHANCER” ROUSES CONCERN

The drug maker *Cephalon* has made an unusual request. It wants the FDA to approve a drug, not for a condition or a disease, but for a symptom—sleepiness. Not just routine sleepiness, but excessive, or “profound sleepiness”—the kind that makes drivers crash.

The drug is modafinil. It is marketed as *Provigil*. It is already approved for the treatment of narcolepsy. Modafinil somehow—no one knows how—targets the hypothalamus and other sleep-regulating areas of the brain. Patients feel more alert without “hyperarousal”.

According to sales figures, more and more sleep experts, psychiatrists, and primary care clinicians are prescribing modafinil for sleepiness for conditions other than narcolepsy. Depression tops the list.

Cephalon's trials reported few adverse effects. A handful of patients discontinued because of headache and nausea. Modafinil induces the P450 system in the liver and may affect metabolism of many drugs. Caution is advised in patients with left ventricular hypertrophy, ischemic heart disease and hypertension. There is an abuse potential. The drug has psychoactive and euphoric effects in some patients.

Modafinil is classified as a schedule IV drug. Long-term studies are limited. The drug blurs the lines between illness and enhancement.

Provigil taken regularly costs several hundreds of dollars per month. The company is ramping up for a marketing blitz which includes direct-to-consumer advertising.

I do not believe primary care clinicians should prescribe this drug. Wait for further experience. RTJ

1-17 SHOPPING ‘TIL WE DROP

This article is based on a collection of essays edited by Allen Kanner and Tim Kasser--*Psychology and Consumer Culture: the Struggle for a Good Life in a Materialistic World*.

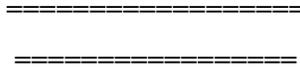
“A culture of consumption, which exalts the acquisition of material goods over almost all other values, is causing severe psychological harm” “People who orient their lives in pursuit of the goals that consumer society tells us to pursue are less happy.”

People who are materialistic report less satisfaction with life, less feeling of vitality, and lower energy compared with those who prize “intrinsic” values (personal development, family relationships, and community involvement). They report more problems with depression, anxiety, and alcohol and tobacco use.

Conversely, people who place a higher value on self-knowledge, family, and friendship, are happier and have higher quality relationships, and a greater sense of freedom.

Since the 1950s, as our economy has grown, happiness has not changed at all. And depression and anxiety have gone up. More wealth is not going to make us happier. It’s about improving other aspects of our world.

I asked myself—Why did I abstract this article? What has it to do with primary care medicine? I am not sure of the answer. Perhaps it may provide some guidance to physicians and their families. It may enable some primary care clinicians to provide guidance to troubled patients. RTJ



“There Is A Widespread Perception Among Parents And Health And Educational Professionals That Young Children Are Spontaneously Active”

1-1 TOTAL ENERGY EXPENDITURE AND PHYSICAL ACTIVITY IN YOUNG SCOTTISH CHILDREN

The epidemic of childhood obesity has been attributed largely to a decline in total energy expenditure (TEE). This study postulated that the lifestyle of contemporary young children is sedentary.

In 1999 and 2000 recruited a socioeconomically representative sample of 78 children aged 3 years. Measured TEE, mean physical activity, and sedentary behavior. Repeated the measurements 2 years later at age 5 in 72 of the children.

At age 3, mean physical activity level and TEE did not differ between sexes. At age 5, mean physical activity and TEE were significantly higher in boys:

| | Age 3 girls | Age 3 boys | Age 5 girls | Age 5 boys |
|---|---------------------------|------------|---------------------------|------------|
| Time spent in sedentary behavior (%) | 81 | 76 | 78 | 73 |
| | Both girls and boys age 3 | | Both girls and boys age 5 | |
| Median time in light-intensity activity (%) | 18 | | 20 | |
| Moderate/vigorous activity (%) | 2 | | 4 | |

Levels of TEE were low at ages 3 and 5 in both sexes, especially in girls. Lifestyles in this sample of youngsters were sedentary. This would increase risk of obesity. Their TEE was significantly lower than the UK estimate average requirement for energy for children.

Children typically spent only 20-25 min per day in moderate to vigorous physical activity. Present recommendations are that they should accumulate at least 60 min daily. “There is a widespread perception among parents and health and educational professionals that young children are spontaneously active. Actually, modern children establish a sedentary lifestyle at an early age.

Prevalence of childhood obesity has increased strikingly in recent years.

Lancet January 17, 2004; 363: 2111-12 First author J J Reilly, University of Glasgow, UK

Comment:

The authors describe sophisticated methods for measuring TEE, physical activity, and sedentary behavior. I did not understand the techniques involved. I took their word for them. See text for details. RTJ

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It Is Extremely Difficult, If Not Impossible, To Maintain A Healthy Bodyweight With A Low Level Of Physical Activity.

1-2 PHYSICAL ACTIVITY AND OBESITY

This editorial comments and expands on the preceding study.

The nature of human physiology is such that it is extremely difficult, if not impossible, to maintain a healthy bodyweight with a low level of physical activity. Technological advances have eliminated many reasons for physical activity. Our environment encourages inactivity. It is unlikely that we can (or want to) change the

environment back to one that requires high levels of physical activity. This means we have to teach children (and adults) to use their intellect to push back against the environment. Such a change can be done by eating a little less and being a little more physically active than ordinarily. Small changes would counter the natural tendency to succumb to the environment.

Obesity arises from an imbalance in which energy intake exceeds energy expenditure. This means that sedentary people must maintain a low intake of energy to avoid obesity. Human physiology did not develop to support restriction of energy intake. It is difficult for most people to do so consistently over time. Our environment encourages energy intake by providing good-tasting, convenient, and inexpensive food. “Sedentary children . . . will probably not be able to maintain energy balance and avoid obesity only by restricting energy intake. Preventing obesity in these children will require both reduction in energy intake and increase in physical activity. “The good news is that it may take only small changes to prevent obesity.”

“Excessive gain in weight can be prevented by small changes in behavior.” The average US citizen is gaining about 2 pounds a year. This gain could occur from as little as 20-50 kcal a day ingested in excess of energy expended. “We suggest that weight gain in 90% of the US adult population could be prevented by reducing positive energy balance by only 100 kcal per day.” This would equate to a little more walking (about 2000 more steps) or eating a few less bites of food (or preferably both). It would take a bit more to change behavior in children. The point is that small and achievable changes in behavior can have a big impact. Walking 2000 additional steps daily and eliminating 100 kcal (eg, drinking water or a diet drink instead of a sugared fizzy drink). Combining these two small changes can save 200 kcal per day. Prevention of obesity is easier than treatment.

Lancet January 17, 2003; 363: 182 Editorial by James Hill, University of Colorado Health Sciences Center, Denver.

Physicians Must Be Aware Of The Costs Of The Drugs They Prescribe.

1-3 “ME TOO” PRODUCTS—FRIEND OR FOE?

A second drug-eluting stent, another drug for erectile dysfunction, another statin drug. Medical journals seem filled with research articles that induce a sense of déjà vu.

Critics assert that these market latecomers often differ trivially from earlier products and that the billions of dollars spent on marketing me-too products could be spent in better ways. They say that these products add little to a physician’s arsenal while driving up the costs of health care.

There is another side to the story. Me-too products create competition among drug and device manufacturers. Competition is a powerful driver for better quality and lower costs. Health care leaders who struggle to provide good care with limited resources see me-too products not as a problem, but as an important part of the solution.

The health care “valuation equation” is sometimes summarized as: Value = $\frac{\text{benefit}}{\text{cost}}$ *

(* or better—benefit/harm-cost RTJ)

The equation is quite useful for understanding how drugs and devices enter the market—or why attempts to bring them to the market may fail. The first product in a new class defines the baseline value equation. The manufacturer may set a high price and may have no trouble selling the product at its asking price. When a second product in the same class comes along, its manufacturers must offer a better value. That product must lead to a better outcome or it must be less expensive. The current monthly costs of statins that are expected to lower LDL-cholesterol by 45% are lower for products that received FDA approval more recently. Costs are also lower for other recently introduced me-too drugs.

Why don't we see real price wars driving health costs much lower? The biggest reason is the rapid rate of medical progress. This causes the value to increase through steady increases in the top half of the equation. A second or third entrant may offer real advantages. At some point, however, technology improves and a new entrant represents only a minimal improvement. At that point, the top part of the equation is frozen, and the action shifts to the bottom. The manufacturer can succeed only by competing on price. The pressure on manufacturers of 3rd and 4th entrants to come up with a product that really improves outcomes or lowers cost will be tremendous.

But manufacturers have learned that physicians and patients are usually reluctant to switch from a medication that is working. So the older drug price may remain high. And the drug company makes larger profits by selling their drug to fewer patients at a high price than they would with more patients paying less.

For market forces to really work, physicians have to choose products as if costs matter.

NEJM January 15, 2004; 350: 211-12 “Perspective”, editorial by Thomas H Lee, Harvard medical School, Boston, Mass

Comment:

Primary care clinicians must be aware of the costs of the drugs they prescribe. Current costs can be easily obtained from drug store's web pages. The cost of a drug containing twice the needed dose may be much less than twice the cost. A pill cutter can save hundreds of dollars yearly. RTJ

Nicotine Causes An Extremely Strong Addiction Very Rapidly

1-4 WHY PEOPLE SMOKE

Cigarette smoking is primarily a manifestation of nicotine addiction. Smokers have individual preferences for their level of nicotine intake. They regulate the way they puff and inhale to achieve their desired nicotine dose. “If it were not for the nicotine in tobacco, people would be little more inclined to smoke than they are to blow bubbles.”

In addition to addiction, social, economic, personal, and political influences all play an important part in determining patterns of smoking prevalence and cessation. Family and wider social influences are often critical in determining who starts smoking, who gives it up, and who continues.

Why do people start smoking?

Experimenting with smoking usually begins in the early teenage years. It is driven predominantly by psychosocial motives. Smoking a cigarette is a symbolic act conveying “I am no longer my mother's child” and

“I am tough”. Children who are attracted to this adolescent assertion of perceived adulthood or rebelliousness tend to come from backgrounds that favor smoking (eg, high levels of smoking by parents, siblings and peers; relatively deprived neighborhoods; schools where smoking is common). They also tend not to be succeeding according to their own or society’s terms. They have impaired self esteem, are overweight, or are poor achievers at school.

The desired image is sufficient for the novice smoker to tolerate the aversion of the first few cigarettes, after which the pharmacological factors assume much greater importance. “As the force from the psychological symbolism subsides, the pharmacological effect takes over to sustain the habit.”* Within a year or so of starting to smoke, children inhale the same amount of nicotine per cigarette as adults, experience craving for cigarettes when they cannot smoke, make attempts to quit, and report experiencing the whole range of nicotine withdrawal symptoms. By age 20, 80% of cigarette smokers regret that they ever started. But, many will continue to smoke for a substantial proportion of their lives. (*All above quotations are from Philip Morris.)

Physical and psychological effects of nicotine:

Absorption of nicotine from the lung is almost instantaneous and complete. With each inhalation an arterial bolus of nicotine reaches the brain faster than by intravenous injection. (See box p 277) Nicotine has a distribution half-life of 15-20 minutes and a terminal half life of 2 hours. Smokers therefore maintain a pattern of repetitive and transient high blood nicotine concentrations from each cigarette. Regular hourly cigarettes are needed to maintain raised concentrations. Overnight, blood levels fall to close to those of non-smokers.

Nicotine activates receptors which are widely distributed in the brain. It induces the release of dopamine. This effect is the same as that produced by amphetamines and cocaine. Nicotine is also a psychomotor stimulant. In new users it speeds simple reaction time and improves performance of tasks of sustained attention. However, tolerance soon develops, and chronic users probably do not obtain absolute improvements in performance, cognitive processing, or mood. Smokers typically report that cigarettes calm them down when they are stressed, and help them concentrate and work more efficiently, but little evidence exists that nicotine provides effective self medication for adverse mood states or for coping with stress.

A plausible explanation for why smokers perceive cigarettes to be calming may come from a consideration of the effects of nicotine withdrawal. Smokers start to experience impairment of mood and performance within hours of their last cigarette, and certainly overnight. These effects are completely alleviated by smoking a cigarette. Smokers go through this process thousands of times over the course of their smoking career. This may lead them to identify cigarettes as effective self relief rather than any absolute improvement.

Symptoms of nicotine withdrawal:

Much of the intractability of cigarette smoking is thought to stem from withdrawal symptoms—irritability, restlessness, feeling miserable, impaired concentration, and increased appetite—as well as craving for cigarettes. These symptoms begin within hours and are maximal during the first week. Most then resolve over 3 to 4 weeks, but hunger can persist for months. Cravings, sometimes intense, can persist for months. Nicotine replacement reliably attenuates the severity of withdrawal.

Social and behavioral aspects:

An intimate coupling of behavior rituals and sensory aspects of smoking with nicotine uptake gives ample opportunity for secondary conditioning. Each puff is linked to the sight of the packet, the smell of the smoke, and the scratch of the throat some 70 000 times each year. Smokers are concerned that if they quit they would not know what to do with their hands.

Other factors encourage smoking: being married to a smoker; being part of a social network in a socially disadvantaged group among whom the prevalence of smoking is so high as to constitute a norm.

The natural course of cigarette smoking is typically the onset of regular smoking in adolescence, followed by repeated attempts to quit. Each year about a third of adult smokers try to quit, usually unaided, and typically relapsing within days. In general, less than 3% of attempts to quit result in sustained cessation.

Regulation of nicotine intake:

Smokers show a strong tendency to regulate their nicotine intakes within narrow limits. They avoid intakes that are too low (withdrawal symptoms), or too high (nicotine overdose). Within individuals, nicotine preferences emerge early and seem to be stable over time. The phenomenon of nicotine titration is responsible for the failure of intakes to decline after switching to cigarettes with low tar and nicotine. Compensatory puffing and inhalation, operating at a subconscious level, ensure that nicotine intakes are maintained. As nicotine and tar delivery in smoke are closely related, compensatory smoking likewise maintains tar intake. This defeats any potential health gain from low tar cigarettes.¹

Socioeconomic status and nicotine addiction.

An emerging phenomenon of the utmost significance is the increasing association of continued smoking with markers of social disadvantage. Affluent persons are much more likely to quit. Smokers who are poor tend to have higher levels of nicotine intake and are substantially more dependent. It is evident that future progress in reducing smoking is increasingly going to have to tackle the problems posed by poverty.

Smoking as a chronic disease:

Cigarette dependence is a chronic relapsing condition that for many users extends over decades. Successful interventions need to tackle the interacting constellations of factors—personal, family, socioeconomic, and pharmacological—that sustain use and can act as major barriers to cessation.

BMJ January 31, 2004; 328: 277-79 “ABC of Smoking Cessation” clinical review by Martin J Jarvis, University College, London

¹ Some have wondered why the nicotine content of cigarettes is not artificially increased in the manufacturing process. This would supply the needed nicotine and automatically lower the intake of carcinogens. Nicotine itself is not carcinogenic.

I presume this would lead to all sorts of ethical and legal complications.

The first article in this clinical review *The Problem of Tobacco Smoking* by Richard Edwards, University of Manchester, UK (*BMJ January 24, 2004; 328 : 217-219*) comments:

Cigarette smoking is one of the biggest avoidable causes of death and disability and one of the biggest threats of current and future world health. “For most smokers, quitting smoking is the single most important thing they can do to improve their

health. Encouraging smoking cessation is one of the most effective and cost effective things that doctors and other health professionals can do to improve health and prolong their patient's lives.

Cessation has substantial and immediate long-term health benefits for smokers of all ages. The excess risk of death from smoking falls soon after cessation and continues to do so for at least 15 years. Former smokers live longer than continuing smokers, no matter what age they stop. Smokers who stop before age 35 have about the same length of life as non-smokers. Stopping before age 30 removes 90% of the lifelong risk of lung cancer. The risk of heart disease decreases quickly after cessation. Within a year, risk is halved. Within 15 years, the risk is almost the same as never-smokers.

Stopping before or in the first 3 to 4 months of pregnancy protects the fetus against the reduced birth weight associated with smoking. Preoperative cessation reduces perioperative mortality and complications.

“Early cessation is especially important.”

Eat More Fish!

1-5 OMEGA 3 FATTY ACIDS AND CARDIOVASCULAR DISEASE—Fishing For A Natural Treatment

Omega 3 fatty acids (**O3FA**) from fish and fish oils can protect against coronary heart disease (**CHD**). In this era of polypharmacy, many persons believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits.

The optimum intake of O3FA is not established. Their method of action is not understood. Some studies report no association, particularly in populations with already moderate fish consumption. Concerns about environmental contamination of fish have been raised.

These investigators performed a literature search and reviewed the evidence regarding associations between O3FA and CHD.

Epidemiological and observational studies:

Over 30 years ago, it was established that Greenland Inuits had a low mortality from CHD despite a diet rich in fat (especially O3FA in fish, seal, and whale). Fatty fish (mackerel, herring, salmon, sardines and trout) are a rich source of O3FA and O6FA. Two to three servings a week should provide about 1 g/d of O3FA.

Most studies have shown an inverse association between fish consumption and CHD. A high concentration of O3FA reduces rate of sudden death. A systemic review of 11 prospective cohort studies concluded that fish intake reduced mortality due to CHD in populations at increased risk.

The Diet and Reinfarction Trial (DART) randomized over 200 men with a recent myocardial infarction. Men who received advice on fish had a 29% reduction in mortality over 2 years, mainly due to a reduction in death from CHD. An Italian study reported a relative risk reduction of 30% in cardiovascular death, and a 45% reduction in sudden death over 3.5 years. Benefits were apparent within 4 months.

Mechanism of action:

Several possible mechanisms have been proposed. None is established. The predominant effect may be antiarrhythmic. O3FA are readily incorporated into atherosclerotic plaques. This may make plaques less vulnerable to rupture. O3FA also have a direct effect on endothelial function. A modest reduction in BP has been reported. O3FA reduce triglycerides in a dose-dependent manner. The reduction may reach 30%. Effects on cholesterol are small.

Clinical implications:

O3FA from fish or fish oil supplements should be considered for *secondary* prevention of patients after MI. Diet should include at least 2 servings of oily fish weekly. Fish oil capsules should be considered for those unable to tolerate fish or are unable to change their diet effectively. “Approved pharmaceutical grade capsules should be prescribed”

The bottom line:

The American Heart Association recommends:

Patients *without* documented CHD should eat a variety of fish (preferably oily) at least twice weekly. Diet should also include vegetable oils.

Patients *with* documented CHD should consume 1 g of O3FA and O6FA daily, preferably from oily fish.

Physicians may prescribe 2-4 g/d of O3FA daily, provided as capsules, for patients with hypertriglyceridemia.

BMJ January 3, 2004; 328: 328-30 “Clinical Review” first author Jahangir N Din, University of Edinburgh, Scotland.

Terminology of *polyunsaturated* fatty acids:

Number of carbon atoms (eg, C18) Number of double bonds (eg, 6) Position of first double bond from CH3 end (eg, n-3; omega 3)

Omega 3 fatty acids

Plant derived: Linolenic acid C18: 3 n-3 Flaxseed, soybean, walnut, and rapeseed (canola) oil

Marine derived: Eicosapentanoic acid C20: 5 n-3 Fish; shellfish

Docosahexanoic acid C22: 6 n-3

Omega 6 fatty acids:

Plant derived: Linoleic acid C18 4 n-6 Corn, safflower, and sunflower oils.

Derived from linoleic acid ;

Arachidonic acid C20 4 n-6

Docosapentanoic acid C22 5 n-6

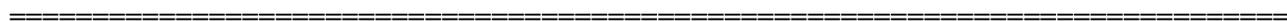
Omega 3 FA and omega 6 FA are essential polyunsaturated fatty acids. O6FA are abundant in the Western diet in the form of vegetable oils rich in linoleic acid. Omega 9 fatty acids are in olive oil, peanuts, avocados, and almonds.

Comment:

Omega 3 and Omega 6 are included in the healthy Mediterranean diet which has been reported convincingly to reduce risk of CHD. Persons *with and without* CHD should consume more fish.

There was a flurry of interest in over-the-counter fish oil capsules about 10 years ago. My pharmacist says that there is still some demand, but it has decreased.

The article presents several websites and reviews. RTJ



Disappointing

1-6 MEMANTINE TREATMENT IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER DISEASE ALREADY RECEIVING DONEPEZIL

The FDA has limited treatment for Alzheimer disease (AD) to monotherapy with anti-cholinesterase inhibitors. In October 2003, the FDA approved memantine for treatment of moderate to severe AD. Memantine is a blocker of the receptor for aspartate. It is a new class of drug.

An open-label study suggested that a combination of memantine with various anti-cholinesterase drugs was well tolerated. This study hypothesized that adding memantine (*Namenda*) to donepezil (*Aricept*) would result in clinical benefit and would be well tolerated.

Conclusion: Memantine resulted in significant statistical, but only slight clinical benefit when added to donepezil. It appeared safe.

STUDY

1. Randomized, controlled trial compared memantine vs placebo in over 400 patients (mean age = 75) All had moderate to severe AD. (Mini-mental State Examination scores 5 to 14. Mean = 10) All were already receiving stable doses of donepezil. (Mean = 10 mg.)
2. Randomized to: 1) Memantine (titrated up to 20 mg dally) + continued donepezil, or 2) Placebo + continued donepezil.
3. Outcome measures included: Measure of change in cognition and activities of daily living, and clinician's + caregiver's impression of change.

RESULTS

1. Changes from baseline over 24 weeks:

| | Baseline | | 24 weeks | |
|---|----------|-----------|----------|-----------|
| | Placebo | Memantine | Placebo | Memantine |
| SIB ¹ | 80 | 78 | -2.4 | + 1.0 |
| ADL ² | 35.8 | 35.5 | -3.3 | -1.7 |
| CIBC-Plus ³ | 4.66 | 4.41 | 4.64 | 4.38 |
| NPI ⁴ | 13.4 | 13.4 | + 2.9 | - 0.5 |
| BGP Care dependency subscale ⁵ | 9.8 | 9.5 | + 2.2 | + 0.6 |

- 1 SIB (severe impairment battery) is a 40-item test to evaluate cognitive dysfunction in patients with more severe AD. Range 0 to 100. Higher levels denote better cognition. Over 6 months, this score of cognitive function did improve, but by only 1.0 points out of 100.
- 2 ADL (activities of daily living) is a 19-item inventory focusing on activities of daily living in later stages of dementia. Possible scores range from 0 to 54—higher scores reflect higher functioning. (Note that this measure *declined* in the memantine group, but not as great as in the placebo group.
- 3 CIBC-Plus (clinicians interview-based impression of change plus caregiver input) assesses the

clinician's impression of effect of medication on overall *clinical* status, and incorporates caregiver observations on a scale from 1 (marked improvement) to 7 (a marked worsening).

(Note that the change in CIBC-Plus in the memantine group was from 4.41 to 4.38 – hardly a clinical benefit. They do state that the P value = 0.03

- 4 NPI (neuropsychiatric inventory) assesses frequency and severity of behavioral symptoms based on an interview with the caregiver. Score ranges from 0 to 144. Higher scores reflect greater symptoms.
- 5 BGP (behavioral scale for geriatric patients) assesses observable aspects of cognition, function, and behavior. (A higher score reflects worse function.)

(The investigators stressed that all differences in outcomes were statistically significant. But, are they clinically significant? They state—“No clinically significant differences were detected between treatment groups in the mean change to end point.” Note the difference in the CIBC-Plus was slight—from 4.41 to 4.38 in the memantine group. (P value = 0.03.) Although statistically significant, hardly of clinical significance.)

2. Adverse effects. Memantine was well tolerated. Adverse effects were similar between groups. Confusion and headache were slightly more common in the memantine group; diarrhea less common. Withdrawals were more common in the placebo group.

DISCUSSION

1. “Efficacy of memantine was significantly better than placebo treatment for treatment of moderate to severe AD in community-dwelling patients. Specifically, measures of cognitive function, activities of daily living behavior, and clinical global status were significantly improved with memantine compared with placebo.”
2. No pharmacokinetic or pharmacodynamic interactions were observed between donepezil and memantine. They act in different ways. Memantine has an effect on the glutamate-aspartate receptor system; donepezil affects cholinesterase
3. The long-term benefits were not addressed by this study.

JAMA January 21, 2004; 291: 317-24 Original investigation, from the Memantine Study Group, first author Pierre N Tatiot, University of Rochester Medical Center, New York

Comment:

Sponsored by Forrest Laboratories. My pharmacy quotes \$155 for a month's supply of memantine (20 mg daily). An interesting sidelight—memantine is a relative of the old drug used for influenza—amantadine.

Memantine has also been reported to lead to benefit in patients with vascular dementia and mixed dementia.

There is evidence that the excitatory effect of glutamate plays a role in the pathogenesis of AD. Memantine is a low-affinity blocker of aspartate receptors. This may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate for memory and learning.

Investigators, as in this report, often stress statistically significant improvement, not clinical improvement. This may be misleading. In my view, the outcome of this study is disappointing. The investigators place a spin on benefits by noting the statistically significant outcomes. This may appear to be an impressive result, but it is not clinically important.

It may be that families will encourage this approach, hoping that their loved one may be an outlier, and receive more benefit.

I would be interested in a study comparing effects of these drugs in patients with mild or possibly beginning AD — those with frequent occurrence of “senior moments” (temporary forgetfulness of names of well-known friends and past events which they recalled immediately when they were younger). RTJ

As “Baby Boomers” Age, Many Will Request Replacement Therapy

1-7 RISKS OF TESTOSTERONE-REPLACEMENT THERAPY AND RECOMMENDATIONS FOR MONITORING.

Review articles are too long to abstract concisely. I enjoy reading them and sometimes abstract a few points which are new to me, which I had forgotten, or which I consider important and deserving emphasis

Hypogonadism is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms: diminished libido and sense of vitality, erectile dysfunction, reduced muscle mass and bone density, depression, and anemia.

It is estimated to affect up to 4 million men in the USA. Prevalence increases with age. Few men receive replacement therapy. About 50% of men over age 80 and 30% of men age 70-79 have low serum levels. (*Defined as a total serum testosterone under 325 ng/dL. Are these “low” levels physiologic or pathologic? I vote for physiologic. RTJ*)

Reports indicate that testosterone replacement may produce a wide range of benefits: improvement in libido, bone density, muscle mass, body composition, mood, erythropoiesis, and cognition.

Recent interest has been fueled by medical awareness of the effects of hypogonadism, media attention regarding hormone replacement, marketing of new topical testosterone formulations, and the desire of “baby boomers” to maintain vigor and health into their more mature years.

Controversy remains regarding indications for testosterone supplementation in aging men. The most controversial topic is the issue of risk. No studies have yet been initiated to assess benefits and risks, especially possible stimulation of prostate cancer. Despite the controversy, prescriptions for testosterone supplementation have increased substantially over the past decade.

This review discusses what is known and not known about regarding risks and to provide recommendations for monitoring men who receive it.

Injectable, transdermal, buccal, and oral formulations are available in the USA. Injectable preparations are typically given at a dose of 100 mg once a week. This produces high peak levels and a “roller coaster” effects on symptoms.

A transdermal-patch preparation is available to deliver 5 to 10 mg. It requires daily application. Relatively uniform blood levels are achieved. Levels above the physiologic range should be discouraged. (*Note this is replacement to the level of younger men, not above. RTJ*)

Oral preparations are discouraged because of adverse effects on the liver.

The author discusses many possible risks especially on benign prostatic hyperplasia (**BPH**) and prostate cancer (**PC**).

BPH: Multiple studies have failed to demonstrate exacerbations of voiding symptoms and residual urine volumes in men receiving replacement therapy. Urinary retention has not occurred at serum levels higher than controls. But, prostate volume does increase significantly during replacement to a level equal to that of men without hypogonadism.

PC: If lowering testosterone levels causes PC to regress, does elevating levels cause PC to appear? Case reports have suggested conversion of an occult PC into a clinically apparent PC. To date, prospective studies have demonstrated a low frequency of association between replacement therapy in hypogonadal men and PC. There has been no follow-up beyond 36 months. It is of some concern that the underlying prevalence of PC in men with low testosterone levels appears to be substantial even in those with a normal PSA and digital rectal examinations.

“Despite decades of research, there is no compelling evidence that testosterone has a causative role in prostate cancer”. There is no compelling evidence to suggest that men with higher testosterone levels are at greater risk of PC or that treating men with hypogonadism with exogenous androgens increases risk.

“In our opinion, proper monitoring with measurement of PSA and digital rectal examination should promote the early diagnosis and thus potential cure of most ‘unmasked’ prostate cancers identified during testosterone treatment.” Certainly all men who present for possible testosterone replacement who are found to have abnormal PSA should undergo biopsy. A rapid rise in PSA or development of an abnormal digital rectal examination during therapy should also indicate biopsy. (The authors advocate routine biopsy in all men presenting for replacement therapy.)

“There is no need to withhold testosterone treatment once a negative biopsy result has been obtained.”
NEJM January 29, 2004; 350: 482-92 Review article, first author Emani Luis Rhoden, Harvard Medical School, Boston Mass.

Comment:

I asked myself if I wasted my time in abstracting these articles. Should primary care clinicians deal with this problem? Should they refer patients seeking therapy to a urologist with considerable experience? At the present stage of development, I would follow the second course.

The value of a therapy has been described as:
$$\text{Value} = \frac{\text{benefits}}{\text{harms-costs}}$$

I believe the benefits are somewhat nebulous and unknown long-term. Harms are potentially great. Cost is considerable considering consultation and laboratory fees as well as the cost of the testosterone. My pharmacy quotes a monthly cost of \$168 for patches delivering 5 mg daily.

Wait Until More Evidence is Available

1-8 HYPOGONADISM IN ELDERLY MEN—WHAT TO DO UNTIL THE EVIDENCE COMES

This editorial comments and expands on the preceding article

A long-awaited report from the Institute of Medicine (IOM) concluded that there is insufficient evidence that testosterone benefits elderly men.

Many studies document that serum testosterone levels decrease as men age. In contrast to the precipitous and profound decrease in estradiol concentrations in women at the menopause, the decrease in testosterone levels in

men occurs moderately and gradually over a period of several decades. (From about 600 ng/dL at age 30 to about 400 at age 80.) One study reported that about 20% of men over age 60 had total serum testosterone below the normal range for young men.

A still unanswered question is whether this decrease is physiologic (perhaps conveying a benefit) or pathologic (causing harm).

In men a reductase converts testosterone to the active androgen, dihydrotestosterone; in women an aromatase converts it to estradiol. Testosterone also acts directly on androgen receptors to affect muscle, bone marrow, bone, and brain. Testosterone has many effects on many tissues

One reason for thinking that the decrease might be pathologic in older men is the parallel between the consequences of frank hypogonadism caused by pituitary and testicular disease and the consequences of aging: decrease in bone density, muscle mass and strength, energy, and libido. In truly pathologic states, administration of testosterone corrects these deficiencies.

Studies in elderly men with low-normal levels have generally shown an increase in lean body mass, a decrease in fat mass, and a trend toward an increase in bone density, but no clear improvement in muscle strength or libido.

Another unanswered question is whether reversing the low-level testosterone in elderly men will exacerbate testosterone-dependent diseases such as prostate cancer, benign prostatic hyperplasia, erythrocytosis, and perhaps sleep apnea. No data answers this question.

For elderly men with low-normal testosterone levels, the IOM has concluded that efficacy has not been demonstrated sufficiently well to justify a *long-term* study to determine risks of testosterone replacement. The committee recommended, as a first step, *short-term* randomized, placebo-controlled studies.

Meanwhile, practicing physicians remain in a quandary. There are a few basic principles for guidance:

The criteria for diagnosis of deficiency should be more stringent in the absence, than in the presence of a disease that is known to cause hypogonadism (eg, pituitary macroadenoma).

Criteria for diagnosis should be more stringent in elderly men. It should be considered if the early morning serum total testosterone is consistently and unequivocally subnormal. (eg, below 200 ng/dL)

When the testosterone level is unequivocally low, the serum leuteinizing concentration should be measured. An elevated level indicates primary (testicular) hypogonadism. A non-elevated level indicates secondary (pituitary) hypogonadism.

Until efficacy and safety of testosterone treatment is established, the prudent course is to limit it to those who are more severely hypogonadal.

Men who are treated should be monitored by serum testosterone levels to ensure relative stability. (Oral therapy should not be used, it is associated with liver dysfunction.) Recipients should also be monitored for possible exacerbation of testosterone-dependent diseases (eg, prostate cancer and hyperplasia).

The response of presenting symptoms is much harder to interpret because symptoms are non-specific.

These principles constitute a “wait until the evidence comes” approach.

Comment:

These recommendations call for a complicated, detailed, and expensive initial investigation and an equally complicated follow-up. I doubt many primary care clinicians would be willing to offer replacement therapy on this basis. RTJ

Helicobacter pylori Has Been Categorized As A Group I Carcinogen.

1-9 HELICOBACTER PYLORI ERADICATION TO PREVENT GASTRIC CANCER IN A HIGH-RISK REGION OF CHINA

“The association between chronic *Helicobacter pylori* (**Hp**) infection and development of gastric cancer (**GC**) is well established.” It has been categorized as a group I carcinogen.

Before the development of adenocarcinoma, the infected gastric mucosa progresses through stages: chronic active gastritis; glandular atrophy; and intestinal metaplasia and dysplasia. All of these changes are precancerous.

This study asked: What is the effect of Hp eradication on prevention of gastric cancer?

Conclusion; Only in the subgroup of subjects *without* precancerous lesions did eradication significantly decrease development of GC.

STUDY

1. Population-based, randomized, placebo-controlled *primary prevention* trial followed 1630 healthy carriers of Hp (mean age = 42) from a high-prevalence area of China. All were endoscoped and biopsied. Of the 1630 patients, 988 (61%) did not have any precancerous lesion.
2. Randomized to: 1) Hp eradication therapy, or 2) Placebo
Eradication therapy consisted of a 2-week course of omeprazole (20 mg), a combination amoxicillin/clavulanate (750 mg), and metronidazole (400 mg)—all twice daily.
3. Outcome measures: Primary = incidence of GC; Secondary = incidence of GC in patients with and without precancerous lesions.
4. Follow-up = mean of 7.5 years.

RESULTS

1. Overall, 18 new cases of GC developed (7 treated; 11 placebo). No significant difference between groups.
2. In the subgroup *without any precancerous lesions* on presentation, none of the treated patients developed GC vs 6 of the placebo treated patients. (P = 0.02)
3. Smoking (hazard ratio = 6.2) and older age (hazard ratio 1.1 per year increment) were independent risk factors for GC.

DISCUSSION

1. Overall, in this primary prevention trial, there was no difference in incidence of GC between groups.
2. In the subset *without any precancerous lesion* there was a significant difference. No patient in the treated group developed GC vs 6 in the placebo group. (P = 0.02)
3. Other studies have reported that Hp eradication can prevent development of a second GC after

endoscopic mucosal resection of early GC.

4. It is still uncertain whether Hp eradication can reverse early precancerous lesions in the stomach. Is there a point of no-return? The investigators believe there is a stage at which changes are not reversible.
5. Other investigators suggest that Hp-infected patients with normal findings on endoscopy are at risk of development of GC. Therefore, in high-risk populations, all patients with *H pylori* infection with no precancerous lesions should consider eradication treatment for gastric cancer prevention.

CONCLUSION

Over 7 years, in a subgroup of patients *without any precancerous lesions* in the stomach, eradication significantly reduced risk of developing GC,

Further studies are required to determine the role of eradication in those with precancerous lesions.

JAMA January 14, 2004; 291: 187-94 Original investigation, first author Benjamin Chun-Yu Wong, University of Hong Kong, China.

Comment:

The authors state that there may be a point of no-return. Ie, once a precancerous lesion has developed, eradication will not reduce risk of gastric cancer.

If I were infected, I would be treated. RTJ

Almost All Neural Tube Defects Can Be Prevented

1-10 FOLIC ACID AND THE PREVENTION OF NEURAL TUBE DEFECTS

Folic acid (FA) supplementation before pregnancy and during its early stages markedly reduces the risk of neural-tube defects (NTD). NTD may be considered to represent a vitamin-deficiency disorder. All women who are planning to become pregnant should take folic acid supplements beginning before pregnancy and continuing through its early stages. Once a pregnancy has been confirmed, it is probably too late.

A study in this issue of NEJM (*January 8, 2004; 350: 134-42*) reported that women who had a pregnancy complicated by NTD had antibodies to folate receptors. This suggests a pathogenesis, and how supplementation may prevent NTD.

What should guide public health policy? At what dose will FA prevent nearly all NTD?

A given dose of FA adds a constant increment to the plasma folate level, irrespective of dietary folate intake. A given percentage increase in the plasma level results in a constant percentage reduction in the risk of NTD. In the background of a serum folate level of 5 ng per mL, which is typical in many Western countries, a dose of about 5 mg per day is expected to decrease the risk of NTD by 85%. Little is gained by higher doses. A dose of 0.4 mg (the amount in a standard multivitamin) reduces risk by an estimated 36%. The average level of food fortification in the USA of about 0.2 mg per day reduces risk of NTD by about 20%. The food fortification level is unnecessarily low. Achieving sufficient levels through dietary change is impractical.

There is no evidence that FA fortification masks B12 deficiency.

A public health policy should include both the mandatory fortification of flour and a recommendation that all women planning a pregnancy take 5 mg a day. Each year about a quarter of a million pregnancies result in the birth of an infant with NTD, or an abortion performed because of such a defect. 85% of them could be prevented if all women took 5-mg daily before pregnancy and during the first trimester.

NEJM January 8, 2004; 350: 101-02 Editorial by Nicholas J Wald, Barts, University of London, UK

Comment:

A high percentage of women of childbearing age have unplanned pregnancies. Since the beginning of pregnancy cannot be determined in these women, I believe a good case can be made to recommend all women at risk for pregnancy routinely take 5 mg FA daily. Primary care clinicians should take the opportunity to so advise their younger women patients regardless of the reason for the consultation.

5-mg folic acid is available only by prescription at a cost of about 10 cents per tablet ~ \$3 a month. Alternatively, over-the-counter six 800 micrograms tablets cost about the same.

The benefit/harm-cost ratio of FA is high. Although overall risk is low, benefit may be great for individuals. The harm is nil. Cost is low. Considering that NTD are devastating for the child and the family, I believe women should be informed and choose if the cost and inconvenience of taking 5-mg daily FA is reasonable. RTJ

Is Adding This Expensive Test Clinically Significant?

1-11 CORONARY ARTERY CALCIUM SCORE COMBINED WITH FRAMINGHAM SCORE FOR RISK PREDICTION IN ASYMPTOMATIC INDIVIDUALS.

Guidelines advise that all adults undergo coronary heart disease (**CHD**) risk assessment to guide preventive treatment.

The Framingham Risk Score (FRS)¹ is a statistical model that uses age, smoking history, blood pressure, cholesterol, HDL-cholesterol, blood glucose levels, and history of diabetes to estimate coronary event risk.

There is a continuing search for additional tests to improve prediction.

This study assessed the coronary artery calcium score (**CACS**) as an additional test to improve prediction.

Conclusion: High CACS, combined with the FRS, can improve risk predictions.

STUDY

1. Entered over 1450 asymptomatic patients (mean age = 65, mostly male) in 1990-92. The great majority had at least one abnormal coronary risk factor which placed them at over 10% estimated 8-year risk of developing coronary heart disease (**CHD**) according to the FRS.
2. None had previous history of CHD or diabetes.
3. At year 3, 1312 surviving participants underwent a second evaluation including a computerized tomography scan (**CT**) to determine presence and extent of coronary calcification.
4. Followed yearly for a median of 7 years after the CT scan. Subjects developing diabetes were

excluded, leaving 1029 to complete the study. These subjects were divided into 4 groups according to their coronary artery calcium score. (CACS range 0 to over 300.)

5. Main outcome measure = non-fatal myocardial infarction (MI) or CHD death.

RESULTS

1. The risk of a non-fatal MI or CHD death in those with a CACS over 300 was 4 times that of participants with a CACS of zero.
2. The risk of a non-fatal MI or CHD death in those with a FRS risk score over 20% was 14 times that of those with a FRS of less than 10%.

| 3. Events | Framingham Risk Score | | | | | | | |
|-----------------|-----------------------|-----|-------|------|-------|-----|---------|------|
| | 0-9 | | 10-15 | | 16-20 | | Over 20 | |
| | E/P* | HR* | E/P* | HR* | E/P* | HR* | E/P* | HR* |
| CACS risk score | | | | | | | | |
| 0 | 0/46 | 1.0 | 2/79 | 1.0 | 5/116 | 3.4 | 7/75 | 7.2 |
| 1-100 | 0/19 | 1.0 | 4/97 | 3.2 | 8/126 | 5.3 | 9/79 | 9.0 |
| 101-300 | 0/14 | 1.0 | 3/40 | 6.2 | 5/64 | 6.2 | 7/53 | 12.5 |
| > 300 | 1/19 | 4.6 | 8/41 | 17.6 | 8/77 | 8.9 | 17/84 | 19.1 |

(*E/P = events/patients * HR = hazard ratio)

DISCUSSION

1. Over a median of 7 years, in asymptomatic patients without diabetes and at least one risk factor for CHD but no prior clinical CHD, the FRS alone was able to rank participants according to CHD event risk in a graded fashion
2. CACS alone was also able to rank CHD event risk independently of the FRS.
3. The CACS significantly modified the risk prediction in all categories of the FRS score of at least 10%, but not when the FRS was less than 10%. When the CRCS was more than 300, the increment in predicted risk was equal to a 3% to 9% increase in the 10-year event risk compared with FRS alone for every category of FRS estimate.
4. The receiver operating characteristic curves, however showed little advantage of FRS + CACS over FRS alone (0.68 vs 0.63).
5. Among the patients with CACS of zero, the absence of CASC did not preclude risk of a CHD event.

CONCLUSION

In this intermediate to high risk cohort with coronary risk factors measured by FRS, a CACS of more than 300 was associated with a significant increase in CHD event risk compared with that determined by FRS alone.

A CACS of zero did not markedly lower risk as predicted by the FRS.

1 Go to: www.nhlbi.nih.gov/guidelines/cholesterol/atglance/pdf for the Adult Treatment III Quick Desk Reference. It contains a copy of the FRS which you can use to determine individual risk.

Comment:

I abstracted this article in detail because some clinicians may become very enthusiastic about adding this expensive risk assessor. The question primary care clinicians must ask is: Would adding CACS determination modify my approach to the patient? I believe it would have no effect. My advice about risk-factor control would remain the same as that predicted by the FRS alone.

Primary care clinicians have a broad base of risk factors to estimate prognosis. We do not yet adequately apply them to individual patients. I do not believe adding another factor will be of any practical advantage. RTJ

1-12 EFFECTS OF AN AD LIBITUM LOW-FAT, HIGH-CARBOHYDRATE DIET ON BODY WEIGHT, BODY COMPOSITION, AND FAT DISTRIBUTION IN OLDER MEN AND WOMEN.

This is a select abstraction of an interesting article. It describes what might be considered the obverse of the Atkins (high fat, low carbohydrate) diet.

The study was based on prior evidence suggesting that high-carbohydrate, low-fat (**HCLF**) diets reduce total energy intake and increase satisfaction.

Conclusion: An ad lib HFLC diet with no attempt at energy intake resulted in weight loss.

STUDY

1. Entered and randomized 24 volunteers age 55 to 80 (mean = 65). All were overweight (mean BMI= 31; weight stable) and sedentary. None were smokers. Some had impaired glucose tolerance. All completed the study.
2. Randomized to a 12-week : 1) HCLF diet, 2) Control diet.
 - 1) HCLF diet consisted of 18% fat; 19% protein; and 63% carbohydrate.
 - 2) Control diet consisted of 41% fat, 14% protein, and 45% carbohydrate.
3. Diets were prepared 3 times daily in a metabolic kitchen and designed to provide 150% of predicted energy requirement. Subjects were instructed to eat as much or as little as they wished.
4. Participants were informed that the purpose of the study was to determine the effects of a heart healthy diet on general disease risk. Thus, there was little overt motivation to lose weight.

RESULTS

| 1. Outcomes over 12 weeks | Control diet | HCLF diet |
|----------------------------|--------------|-----------|
| Energy intake (kcal/d) | 2825 | 2250 * |
| Protein (% of energy) | 15% | 19% |
| Fat (% of energy) | 41% | 18% |
| Carbohydrate (% of energy) | 45% | 63% |
| Body weight loss | -0.1 kg | -3.2 kg |

(* Note the difference in energy intake between groups both of which were instructed to eat as much as they desired. Why the difference? I suspect it was due in part to the monotony of the HCLF diet. RTJ.)

2. No change between groups in resting metabolic rate or fat oxidation.

DISCUSSION

1. Ad-lib consumption of this HCLF diet over 12 weeks resulted in significant loss of body weight
2. The HCLF diet was not an eat-any-carbohydrate you wish. It consisted mainly of complex carbohydrates.

| | |
|-------------------|--|
| Breakfast | Cereal |
| Lunch and dinner | Vegetarian chili, lentils, carrots, boiled potato, rice, beans, spaghetti with tomato sauce Some meat: sliced ham, baked chicken breast, hamburger patty, baked fish, tuna. |
| Breads | Blueberry muffin, whealtbagel, English muffin, whole wheat bread, cornbread |
| Sweets and snacks | Lemon pudding, crispbread crackers, popcorn |
| Fruit | Variety |
| Vegetables | Variety |
| Beverages | Apple juice, cranberry juice, orange juice, |
| Dairy products | Skim milk, non-fat yogurt, shredded cheddar cheese, mozzarella cheese. |

3. Despite being fed to maintain body weight, individuals complained that they were given too much food. They were never hungry.
4. “Low-fat, high-carbohydrate diets may reduce body weight via reduced food intake, since complex carbohydrate-rich foods are more satiating and less energy dense than higher-fat foods.”

Archives Int Med January 26, 2004; 164: 210-17 Original investigation, first author Nicholas P Hays, University of Arkansas for Medical Sciences, Little Rock.

Comment:

Dr. William J Evans, one of the investigators, kindly e-mailed me a list of foods provided.

Food choices in the HCLF diet were limited—no sweets and few desserts allowed. I doubt many free-living overweight persons would adhere to the diet for very long.

I consider this an interesting, but not a clinically significant study. It was performed under strict observation. Food was provided by a metabolic kitchen. It lasted only 12 weeks. There were few subjects.

Weight-loss diets have become a multimillion dollar industry. There are many types of diet and approaches to dieting. Overweight persons in the USA seek a quick fix. There is none. None of the diets consistently works over time. Most individuals gradually gain back any weight lost, regardless of the diet.

A calorie is a calorie, is a calorie, is a calorie. RTJ

1-13 THE EFFECTS OF STRONTIUM RANELATE ON THE RISK OF VERTEBRAL FRACTURE IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS

Vertebral deformities in women with osteoporosis predict further vertebral fractures.

The bone fragility characterizing osteoporosis after the menopause results from an imbalance in bone remodeling causing bone resorption to exceed bone formation. Antiresorptive therapies reduce the rate of remodeling and lower fracture rate. The increase in bone mineral density observed in clinical trials of these drugs is the result of more complete secondary mineralization of the existing (but reduced) bone tissue mass.

Restoration of bone tissue mass and bone structure is not achieved with antiresorptive drugs. This requires use of anabolic agents.

Strontium ranelate ¹ (SR) is an orally active agent now proposed for treatment of osteoporosis. It consists of two atoms of strontium and an organic moiety. It acts in a dual manner to stimulate formation of new bone and decrease bone resorption .

To date, no deleterious effects on mineralization of bone have been reported.

This study assessed the efficacy of SR against vertebral fractures in postmenopausal women with osteoporosis. And its safety.

Conclusion: Treatment led to early and sustained reductions in risk of vertebral fractures.

STUDY

1. A phase 3 trial randomized to over 1600 postmenopausal women (mean age 69; mean 21 years since menopause). All had osteoporosis (mean T score = -3.5) and a history of at least one minimal-trauma vertebral fracture. All received a run-in period of 2 to 24 weeks of calcium and vitamin D, depending on severity of deficiency.
2. Randomized to: 1) 2 g of oral SR daily, or 2) placebo
3. All received supplementary calcium and vitamin D.
4. X-rayed vertebra and measured bone mineral density (BMD) periodically. BMD at the lumbar spine was measure by dual-energy x-ray absorptiometry and adjusted for strontium content.²
5. Follow-up = 3 years.

RESULTS

1. About 1400 women made up the population of the intention-to-treat analysis.

| 2. Outcomes at 3 years: | Strontium | Placebo | NNT* |
|--------------------------------------|-----------|---------|------|
| New vertebral fractures | 18% | 28% | 10 |
| More than one new vertebral fracture | 6.4% | 9.8% | 29 |
| Symptomatic vertebral fractures | 11.3% | 17.4% | 16 |
| Reported back pain | 17.7% | 21.3% | 28 |

(* Number of patients needed to treat for 3 years to prevent one fracture or back pain.)

2. Over 3 years fewer patients in the strontium group lost at least 1 cm in height.

3. No difference in non-vertebral fractures.
4. Adjusted for strontium content², bone mineral density at the lumbar spine increased over base-line in the strontium group by 6.8% vs a decrease of 1.3% in the placebo group
5. The strontium group had an increase in the serum bone-specific alkaline phosphatase (increased bone formation) and a lower concentration of C-telopeptide (decreased resorption) compared with placebo.
6. Adverse effects: There were no significant differences between groups in the incidence of serious adverse effects. Diarrhea was more common in the SR group (6%). Withdrawals were similar. There was no change in vitamin D metabolites.

DISCUSSION

1. SR decreased risk of new vertebral fractures at one year and at 3 years.
2. The reduction was similar to that reported from alendronate and risedronate. And slightly lower than the reduction with parathyroid hormone, a bone-forming drug. .
3. The authors suggest, on the basis of blood levels of biochemical markers, that SR acts by a combination of increasing bone formation and decreasing bone resorption.

CONCLUSION

SR treatment of postmenopausal osteoporosis led to early and sustained reductions in risk of vertebral fractures.

NEJM January 29, 2004; 350: 459-68 Original investigation, first author Pierre J Meunier, Edouard Herriot Hospital, Lyons, France.

- 1 Strontium was originally detected in lead mines near Strontian, Scotland in the late 1700s.
- 2 Any metal with an atomic number greater than calcium can influence BMD. The atomic number of strontium is 38; calcium, 20. My brief search failed to find the formula for ranelic acid.

Comment:

There was a flurry of interest in fluoride several years ago. Enthusiasm decreased because bone became more fragile. There was no indication of this association with SR in this study. I spent the considerable time to abstract this study because of its potential importance as an effective, safe and likely inexpensive therapeutic agent. Primary care clinicians be on the lookout for developments RTJ

An editorial in this issue of NEJM (pp 504-06) by Ghada El-Hajj Fuleihan, American University of Beirut Medical Center, Lebanon. comments and expands:

Strontium is present in trace amounts in food and water, and throughout the skeleton. Areas of active osteogenesis take up a large percent of strontium.

Strontium was used years ago for osteoporosis. It fell out of favor because mineralization defects were detected and synthesis of calcitriol was inhibited. These adverse effects were thought possibly due to calcium-deficient diets and the doses used. In the past decade interest has been renewed.

In contrast to other therapies for osteoporosis, strontium appears to induce uncoupling of bone remodeling, simultaneously stimulating bone formation and reducing bone resorption.

“The current trial establishes the efficacy of strontium ranelate, a familiar element relaunched as a new compound, in reducing the risk of vertebral fractures and its role in the armamentarium of therapy for osteoporosis.”

Low-Dose Aspirin Effectively Prevents Major Thrombotic Complications

1-14 EFFICACY AND SAFETY OF LOW-DOSE ASPIRIN IN POLYCYTHEMIA VERA

The increase in the red cell mass in polycythemia vera (**PV**) causes hyperviscosity of the blood, a major determinant of circulatory disturbance. Thrombotic complications are a major cause of illness and death in untreated patients. Chemotherapy and phlebotomy are used in patients at high risk of thrombotic events.

PV is associated with an increase in thromboxane synthesis. This suggests that thromboxane-dependent platelet activation is a major cause of thrombosis.

This study assessed the effect of low-dose aspirin on risk of thrombotic complications in patients with PV.

Conclusion: Low-dose aspirin prevented thrombotic complications.

STUDY

1. A randomized, double-blind, placebo-controlled trial enrolled over 500 patients (mean age 60) with PV to assess the efficacy and safety of low-dose aspirin. None had conditions which called for antithrombotic therapy.
2. At baseline: mean hematocrit = 49; red-cell count = 5900; white-cell count = 10,500; platelet count = 380 000.
3. Over 50% had been treated with phlebotomy and/or chemotherapy.
4. Randomized to: 1) 100 mg enteric-coated aspirin daily, or 2) placebo
5. End-points: A) Cumulative rate of non-fatal myocardial infarction (**MI**), non-fatal stroke, or death from cardiovascular causes; B) Cumulative rate of non-fatal MI, non-fatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes.
6. Follow-up at intervals up to 60 months. (Mean = 3 years.)

RESULTS

1. Compared with placebo, aspirin was associated with a reduced risk of end-point A (relative risk = 0.41), and a reduced risk of end-point B. (RR= 0.40).
2. Overall mortality and cardiovascular mortality were not reduced significantly.
3. Incidence of major bleeding episodes were increased in the aspirin group.

| 4. Endpoints: | Aspirin (%) | Placebo (%) | Absolute difference (%) | NNT |
|-------------------|-------------|-------------|-------------------------|------------|
| Primary A | 2 | 4.9 | 2.9 | 34 |
| Primary B | 3.2 | 7.9 | 4.7 | 21 |
| 5. Major bleeding | 9.1 | 5.3 | 3.8 | 26 (harm)* |

(* P value = 0.08; relative risk = 1.6, CI = (0.27 to 9.71))

DISCUSSION

1. The rationale for this trial was based on 3 considerations:
 - 1) Synthesis of platelet thromboxane is increased in PV.
 - 2) Low-dose aspirin effectively suppresses platelet thromboxane
 - 3) A previous trial found low-dose aspirin well-tolerated.
2. Most patients enrolled in this trial had no previous thrombotic events. The trial can be considered a *primary prevention* trial.
3. The benefit of aspirin was detectable after about 180 days.
4. Patients with PV have an increase in the synthesis of thromboxane by a factor of approximately 10. This can be largely suppressed by low-dose aspirin. The authors believe the increased production of thromboxane is the primary target of aspirin.
5. An important finding was the moderate increase in the risk of bleeding. (RR= 1.6) This is consistent with previous observations. Nevertheless, the authors recommend the use of aspirin to prevent thrombotic complications in patients with PV.

CONCLUSION

Long-term, low-dose aspirin safely prevented thrombotic complications in patients with PV.

NEJM January 8, 2004; 350: 114-24 Original investigation by the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) investigators, first author Raffaele Landolfi, Catholic University School of Medicine, Rome, Italy.

Comment:

Low-dose aspirin should be routinely advised for patients with PV who have no contraindication. The benefit/harm-cost ratio is high.

Aspirin, even in low-dose is associated with an increased risk of bleeding. (Note the skewed confidence interval—0.27 to 9.71.) Once a major bleed has occurred, further aspirin is contraindicated.

PV is the most common of the chronic myeloproliferative disorders. Primary care clinicians will likely refer patients to a hematologist, but may be responsible for long-term follow-up. RTJ

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1-15 DAILY ASPIRIN—ONLY HALF THE ANSWER

This editorial comments and expands on the preceding study.

The long-term consequences of the unregulated hematopoiesis in patients with polycythemia vera include: extramedullary production of blood (liver and spleen), painful and debilitating organomegaly, portal hypertension, hyperuricemia and secondary gout, renal stones, pruritus, hemorrhage (usually mucocutaneous), and thrombosis. Myelofibrosis, bone marrow failure, and acute leukemia may ensue. Chemotherapy with alkylating agents is associated with malignant transformation.

Thrombosis causes much of the illness and death. No part of the vascular system is spared. There is a predilection for peripheral arterioles and cerebral and abdominal vessels. Thrombosis develops in about 40% of

patients, most often before or at the time of diagnosis. Rates of fatal thrombosis may be high. Most arterial thrombi occur in small vessels and can cause erythromelalgia and ocular migraine. PV also is a leading cause of hepatic vein thrombosis. Attempts to control erythrocytosis by phlebotomy often fail to diminish the high rate of thrombosis.

PV is unique among conditions causing erythrocytosis. The increase in red cell mass is accompanied *not* by a reduction in plasma volume, but often by an expansion. It is not possible to estimate the red-cell mass on the basis of the hematocrit. An apparently normal hematocrit may *not* be normal in patients with this disease.. A safe target is under 45% in men and under 42% in women. Viscosity of the blood rises dramatically at hematocrit levels above 45%.

Platelet activation and utilization in PV are increased. Neutrophils and endothelial cells are also activated. Release of the von Willebrand factor provides the final component for inappropriate initiation of coagulation.

The microvascular syndromes (erythromelalgia and ocular migraine) are independent of blood viscosity. They arise from widespread platelet and endothelial activation, facilitated by the high shear rate in arterioles. Platelet aggregates form on endothelial cells. Aspirin arrests this process.

Increased blood viscosity is a paramount cause of large-vessel arterial and venous thrombosis. It is in the large vessels that the negative effect of high hematocrit is most pronounced. But endothelial cell activation is also important.

NEJM January 8, 2004; 350: 99-101 Editorial by Jerry Spivak, Johns Hopkins University school of Medicine, Baltimore MD.

Comment:

What is the normal range of hematocrit? Authorities do not agree. Normal range according to:

| | Female (%) | Male (%) |
|------------|------------|----------|
| SI units | 33-43 | 39-49 |
| NEJM | 37-48 | 42-52 |
| Dictionary | 37-47 | 42-52 |

1-16 POISED TO CHALLENGE NEED FOR SLEEP, “WAKEFULNESS ENHANCER” ROUSES CONCERN

The drug maker *Cephalon* has made an unusual request. It wants the FDA to approve a drug, not for a condition or a disease, but for a symptom--sleepiness. Not just routine sleepiness, but excessive, or “profound sleepiness”--the kind that makes drivers crash.

The drug is modafinil. It is marketed as *Provigil*. It is approved for the treatment of narcolepsy. Now, about 90% of prescriptions are going for off-label uses. A *Washington Post* article recently recommended it for jet-lag. A *New Yorker* author found it helpful for late-night writing marathons. A world champion sprinter took it before a race. A TV commentator commented that when taking it “I feel quite awake. I don’t feel the heart racing thing that caffeine sometimes does. A bit jumpy, a bit extra something going on here”.

The FDA's central nervous system advisory committee was less than enthusiastic about Cephalon's request. It did give the go-ahead to include indications for two new diagnoses--obstructive sleep apnea, and shift-work sleep disorder. It did not endorse use in patients with other causes of sleepiness. There was concern that patients may view it as a replacement for the normal amount of nighttime sleep. "We would never advocate that there is a substitute for sleep." The FDA rebuked *Cephalon* for running advertisements that provided the "overwhelming misleading impression that *Provigil* can be used to improve wakefulness in all patients presenting with symptoms of daytime sleepiness. But according to sales figures, more and more sleep experts, psychiatrists, and primary care clinicians are prescribing modafinil for sleepiness not caused by narcolepsy. Depression tops the list.

What about adverse effects? "It's the drugs safety record that is winning over clinicians." *Cephalon's* trials reported few adverse effects. A handful of patients discontinued because of headache and nausea. A jittery feeling was less frequent than in patients taking methylphenidate (*Ritalin*). Amphetamines work by revving up the entire body, increasing BP and heart rate. Modafinil somehow--no one knows how--targets the hypothalamus and other sleep-regulating areas of the brain. Patients feel more alert without "hyperarousal". Modafinil is classified as a schedule IV drug. It has some abuse potential. Long-term studies are limited. The drug blurs the lines between illness and enhancement.

The drug is cleared from the blood quickly enough so that shift workers can sleep when they are ready. Outside the laboratory, sleep specialists say that they have repeatedly seen modafinil rejuvenate miserable patients. But all the sleep experts interviewed expressed concern that patients and physicians will confuse modafinil's symptom relief with a treatment for the underlying condition. Chronic short sleepers are at higher risk for cardiovascular problems, hypertension, heart failure and stroke. They have a higher overall mortality rate.

Provigil costs several hundreds of dollars per month. The company is ramping up for a marketing blitz which includes direct-to-consumer advertising.

JAMA January 14, 2004; 168-70 "Medical News and Perspectives", commentary by Brian Vastag, JAMA Staff.

Comment:

I felt that the article overall would lead to greater use rather than discouraging it.

My PDR gives additional information:

The blood concentration reaches a steady state in 2 to 4 days. The half life is 15 hours. I wonder--how does this jive with the statement in the text that the drug is cleared fast enough so that shift workers can sleep when they are ready?

Modafinil induces the P450 system in the liver and may affect metabolism of many drugs.

Caution is advised in patients with left ventricular hypertrophy, ischemic heart disease and hypertension.

There is an abuse potential. The drug has psychoactive and euphoric effects in some patients.

I do not believe primary care clinicians should prescribe this drug. Wait for further experience. RTJ

Earn As Much As You Can; Save As Much As You Can; Give As Much As You Can.

1-17 SHOPPING 'TIL WE DROP: *Can Psychology Save Us From Our Lust For Possessions?*

(This article is based on a collection of essays edited by Allen Kanner and Tim Kasser--*Psychology and Consumer Culture: the Struggle for a Good Life in a Materialistic World*)

“A culture of consumption, which exalts the acquisition of material goods over almost all other values, is causing severe psychological harm. Yet it is ignored by the psychology profession.”

Consumption is one of the most important psychological issues of our times, but it is getting scant attention. The profession prefers to deal with problems at the level of individuals, families, and small groups, not culture. There is a social taboo against criticizing capitalism in the USA. This prevents psychologists from objectively looking at the harm that is being done by the current economic and social system. The profession of psychology has been deeply involved in the creation of the consumer culture of today—in particular by helping to create modern marketing techniques.

To make the case that consumerism is worthy of psychology’s attention, the editors have been applying the methods used to study disorders such as depression and anxiety to assess the relation between the importance that people place on material values and their sense of happiness and well-being. “The basic finding is that people who orient their lives in pursuit of the goals that consumer society tells us to pursue are less happy.”

To be happy, people need to feel safe and secure. They need to feel competent and able to do the things they need to do. They need to feel connected to people and loved. They need to feel free and autonomous.

These values are not often advertised much in society, except as a way to sell something.

Most research shows that people who place a high value on attaining financial success, having nice possessions, and having the right image and high status based on wealth and possessions score lower on several measures of well-being. People who are materialistic report less happiness, less satisfaction with life, less feeling of vitality, and lower energy compared with those who prize “intrinsic” values (personal development, family relationships, and community involvement). They report more problems with depression, anxiety, and alcohol and tobacco use.

Conversely, people who place a higher value on self-knowledge, family, and friendship, are happier and have higher quality relationships, and a greater sense of freedom.

Some psychologists disagree. They say that the desire for more material things is associated with poor mental health only when it is associated with certain motives—the desire for power or “lording it over” others; a desire to show off, prove yourself, and to show that you are not as stupid as everyone says you are. These motives are all rooted in self-doubt. There are many healthy motives for acquiring wealth—to attain financial security; provide for your family, and your children’s education; to enjoy a comfortable life; and to buy goods you personally enjoy. “It is not the desire for goods as such that is bad for people, but it’s desiring them for the wrong reasons.”

Some people are more vulnerable to materialistic appeals than others—in particular people who come from poorer backgrounds, from broken homes, and from families in which the parents are cold and controlling. These people are insecure. If you want to feel secure, buy this, become rich, latch on to materialistic values as a way to feel good about yourself

Material things may help you feel good (or less bad) for a little while, but they don’t do anything to solve the underlying problem.

Since the 1950s, as our economy has grown, happiness has not changed at all. And depression and anxiety have gone up. More wealth is not going to make us happier. It’s about improving other aspects of our world.

Lancet January 24, 2004; 363: 296-97 Feature article by Michael McCarthy, Lancet staff.

Comment:

I asked myself—Why did I abstract this article? What has it to do with primary care medicine? I am not sure of the answer. Perhaps it may provide some guidance to physicians and their families. It may enable some primary care clinicians to provide guidance to troubled patients.

I believe many people, young and old, are adopting a more caring, less materialistic lifestyle. They are opting for spending more time with family and in community service. And placing less value on owning the biggest house, and the most expensive automobiles.

Some time ago I read a short 3-item suggestion for pursuing a good lifestyle: 1) Earn all you can
2) Save all you can 3) Give all you can. (*I wish I could remember where I read it. RTJ*)

Earning requires you to obtain the best education and training possible, and then to apply it honestly in the workplace. The goal is to secure a safe, comfortable home; to educate your children; and to provide for your continuing independence in old age.

Saving means not living ostentatiously—living “below your means”; not being profligate, but conserving.

Giving is the hardest—at least giving wisely. There are multitudes of causes which will make good use of your gifts and time for the general welfare. I believe you should give as much as you can to your children in time of need, and a legacy large enough to help them get them started on the same path you have trod—but not enough to deter them from earning their own way through life. RTJ

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Best wishes,

Richard James Editor/publisher