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GLYCEMIC INDEX; GLYCEMIC LOAD

SCREENING FOR DEPRESSION

“WHAT SHOULD I DO, DOC?” Helping Patients Decide.

ALENDRONATE IMPROVES BONE MINERAL DENSITY IN ELDERLY WOMEN

THERAPEUTIC EQUIVALENCE OF ALENDRONATE 70 MG ONCE-WEEKLY

SAFETY OF NEWLY APPROVED DRUGS

PUBLIC EXPECTATIONS AND ATTITUDES FOR ANNUAL PHYSICAL EXAMINATIONS

TYPE 2 DIABETES IN PREGNANCY: A Growing Concern

HEAD LICE

EFFECTS OF MODERATE ALCOHOL INTAKE ON FASTING INSULIN AND GLUCOSE

SEXUAL DYSFUNCTION IN MEN AFTER TURP

AZITHROMYCIN FOR ACUTE BRONCHITIS

SELECTIVE COX-2 INHIBITORS, NSAIDs, ASPIRIN, AND MYOCARDIAL INFARCTION

IMMEDIATE REPAIR COMPARED WITH SURVEILLANCE OF SMALL ABDOMINAL AORTIC ANEURYSMS

PENTOXIFYLLINE FOR TREATMENT OF VENOUS LEG ULCERS

HORMONAL THERAPY FOR GASTROINTESTINAL ANGIODYSPLASIA

FONDAPARINUX

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EDITED BY RISHARD T. JAMES JR. MD

400 AVINGER LANE #203

DAVIDSON NC 28036 USA

rjames6556@aol.com

HIGHLIGHTS MAY 2002

5-1 THE GLYCEMIC INDEX

The rate of carbohydrate absorption after a meal, as quantified by the glycemic load (GL) has significant effects on postprandial hormonal and metabolic responses. High GL meals produce an initial period of high blood glucose and insulin levels. This may be followed by reactive hypoglycemia, counter-regulatory hormone secretion, and elevated free fatty acid concentrations. These events may promote excessive food intake, beta cell dysfunction, dyslipidemia, and endothelial dysfunction. As a result, the risk of obesity, type 2 diabetes, and heart disease increases – a hypothesis that derives considerable support from clinical trials and epidemiological analyses.

Despite controversy, clinical use of GL as a qualitative guide to food selection is prudent in view of the preponderance of evidence suggesting benefit and absence of adverse effects.

5-2 SCREENING FOR DEPRESSION

Asking two simple questions about depressed mood detects a majority of depressed patients, and in some cases performs better than the original instruments from which they were derived:

1. "Over the past 2 weeks have you felt down, depressed, or hopeless?"
2. "Over the past 2 weeks have you felt little interest or pleasure in doing things?"

5-3 "WHAT SHOULD I DO, DOC?" Helping Patients Decide.

Patients often ask their physician – "What would you do if you had my condition?"

Physicians may reply – "This is your decision to make. The right choice depends on your preferences."

Getting patients involved in their medical decisions can often be challenging. Decisions are almost never value neutral.

5-4 ALENDRONATE IMPROVES BONE MINERAL DENSITY IN ELDERLY WOMEN WITH OSTEOPOROSIS RESIDING IN LONG-TERM CARE FACILITIES

Alendronate increased BMD in women past age 79.

5-5 THERAPEUTIC EQUIVALENCE OF ALENDRONATE 70 MG ONCE-WEEKLY AND ALENDRONATE 10 MG DAILY IN THE TREATMENT OF OSTEOPOROSIS

Alendronate once weekly will provide patients with a more convenient, therapeutically equivalent alternative dosing schedule.

Practical point: Periodic, instead of daily administration, will likely become the norm.

5-6 SAFETY OF NEWLY APPROVED DRUGS.

How reluctant should the primary care clinician be to prescribe a new drug? Certainly, by history, physicians have reason for concern about undiscovered toxicities. Even long-marketed drugs sometimes are shown to have unexpected toxicities. "There is no duration of use that allows a physician complete assurance that additional toxicity will not emerge." But it is incorrect to describe the introduction of unsafe drugs as frequent.

Physicians contemplating prescribing a new drug should consider carefully the reason for the choice, particularly when an equally effective alternative is available. If there is sound reason to use a recently approved drug, there is no need to deny patients the treatment.

5-7 PUBLIC EXPECTATIONS AND ATTITUDES FOR ANNUAL PHYSICAL EXAMINATIONS AND TESTING.

The public has high expectations for a comprehensive annual physical examination and extensive routine testing. The expectations are modified by costs.

Over the past 3 decades, most major medical organizations have changed recommendation for a scheduled complete physical examination to recommend selective preventive services in the context of visits for other reasons.

The public needs education about the value of periodic health examinations and current recommendations for specific preventive health services.

5-8 TYPE 2 DIABETES IN PREGNANCY: A Growing Concern

The higher rates of type-2 diabetes in pregnancy bring with them higher rates of maternal and fetal morbidity, and might even contribute to the increasing incidence of type-2 diabetes. Better recognition of this growing entity by primary care physicians who see these patients before pregnancy, and a heightened awareness of the need for pre-pregnancy counseling about preconception glycemic control would lead to less morbidity and mortality from congenital anomalies.

Practical point: Primary care clinicians have the responsibility and opportunity to reduce likelihood of development of type-2 diabetes in adolescents and young women. Those at risk should be screened by post-glucose challenge (glucose intolerance; post challenge blood glucose above 140). Education and reduction of risk may avert a tragedy.

5-9 HEAD LICE

Is exclusion from school necessary? Transmission does occur between pupils. Exclusion is almost universally practiced. However, because the infestation in a child has probably been present for weeks before detection, a few extra hours of exposure will probably make no difference in risk of transmission. "Exclusion from school based on the presence of lice or nits is *not* recommended by the American Public Health Association."

"Excluding children from school because of head lice results in anxiety, fear, social stigma, overtreatment, loss of education, and economic loss if parents miss work – a classic case of the cure being worse than the disease."

5-10 EFFECTS OF MODERATE ALCOHOL INTAKE ON FASTING INSULIN AND GLUCOSE CONCENTRATIONS AND INSULIN SENSITIVITY IN POSTMENOPAUSAL WOMEN.

Consumption of 30 g/d of ethanol had beneficial effects on fasting insulin, insulin sensitivity, and triglyceride concentrations in non-diabetic postmenopausal women. This was independent of body mass index.

5-11 SEXUAL DYSFUNCTION IN MEN AFTER TREATMENT FOR LOWER URINARY TRACT SYMPTOMS

Assertions that minimally invasive treatment such as laser therapy may have less impact on sexual function seem to be unjustified. Compared with laser, TURP had a beneficial effect on aspects of sexual function – particularly in improving erectile dysfunction and reducing pain on ejaculation.

Older men who need treatment for troublesome lower urinary tract symptoms and who wish to retain (or even improve) sexual function may consider TURP.

5-12 AZITHROMYCIN FOR ACUTE BRONCHITIS

Azithromycin was no more effective than low-dose vitamin C for treatment of acute bronchitis in adults.

5-13 SELECTIVE COX-2 INHIBITORS, NSAIDs, ASPIRIN, AND MYOCARDIAL INFARCTION

Use of naproxin was associated with a reduced rate of acute myocardial infarction. There is no evidence that use of COX-2 inhibitors increases (or decreases) the risk of myocardial infarction.

The effects noted are due to the anti-platelet, anti-thrombotic actions of naproxin, rather than a detrimental effect of COX-2 inhibitors.

The investigators concluded that there was no evidence for excess cardiovascular events in patients treated with rofecoxib compared with those treated with placebo or NSAIDs other than naproxin. The difference in outcomes was likely due to an antiplatelet effect of naproxin.

5-14 IMMEDIATE REPAIR COMPARED WITH SURVEILLANCE OF SMALL ABDOMINAL AORTIC ANEURYSMS

Survival was not improved by elective repair of AAA smaller than 5.5 cm. The study supports a policy of reserving elective repair for those at least 5.5 cm in diameter.

5-15 PENTOXIFYLLINE FOR TREATMENT OF VENOUS LEG ULCERS

These results suggest that pentoxifylline gives benefits in addition to compression for venous leg ulcers. It is possibly beneficial when used alone.

5-16 HORMONAL THERAPY FOR GASTROINTESTINAL ANGIODYSPLASIA

Results were uniformly negative for a beneficial effect of hormones. Interventional therapy is required.

5-17 FONDAPARINUX: A New Synthetic Pentasaccharide For Thrombosis Prevention

A new anticoagulant (fondaparinux) is becoming available. This synthetic compound is almost identical to the natural pentasaccharide sequence of heparin. It inhibits factor Xa.

Practical point: None new. Watch for developments.

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Physiological Mechanisms Relating to Obesity, Diabetes, and Cardiovascular Disease.

5-1 THE GLYCEMIC INDEX

All dietary carbohydrates, from starch to table sugar, share a basic biological property -- they can be digested and converted into glucose. Digestion rate, and therefore blood glucose response, is commonly thought to be determined by saccharide chain length. This gave rise to the terms “complex carbohydrate” and “simple sugar”.

Throughout the past 25 years, the relevance of chain length in carbohydrate digestion has been questioned. Marked differences in glycemic and insulinemic responses to ingestion of isoenergetic amounts of various foods (eg, white bread vs pasta) were noted. The term “glycemic index” was proposed to classify carbohydrate-containing foods according to their glycemic response.

This article examines the hormonal and metabolic events following consumption of foods whose glycemic index differs.

Glycemic index: A physiological basis for classifying carbohydrate.

Glycemic *index* (**GI**) is defined as the incremental area under the glucose response curve for 2 hours after a standard amount (50 gm) of carbohydrate from a test food relative to a control food (eg, white bread). It is determined primarily by the nature of the carbohydrate and other factors that affect digestibility and insulin secretion. GI values for common foods differ by more than 5-fold. In general, starchy foods eaten in the USA have a high GI. Non-starchy vegetables, fruits and legumes have a low GI.

Examples of the comparative glycemic response to various foods. To determine the glycemic index, each portion of food consumed contains 50 g of available carbohydrate:

Glycemic Index (**GI**) 50 gm carbohydrate serving

Baked potato	85
Corn flakes	84
White bread	70
Carrot	71
Milk	27
Peanuts	14

Regular consumption of high-GI meals results in higher average 24 hour blood glucose and insulin levels as compared with low-GI foods. Higher C-peptide and HbA1c levels result in non-diabetic as well as diabetic individuals.

Glycemic load: (GL)

Glycemic *load* is a weighted average.

The glycemic load is the plasma glucose response (area under the glucose response curve) to the carbohydrate contained in a *usual serving* of the food. (As compared with the 50 gm carbohydrate serving.)

GL of individual foods is a weighted average GI. (Ie, the GI multiplied by grams of carbohydrate per usual serving size.) [*Note the difference between glycemic index and glycemic load.*]

	Glycemic Load (GL)--usual serving	Serving size
Baked potato	20	110 gm
Corn flakes	21	225 mL
White bread	21	2 slices
Carrot	4	55 gm
Milk	6	225 mL
Peanuts	1	30 gm

The glycemic load for most non-starchy vegetables is too low to measure.

Thus, a carrot has a high GI, but a low GL: a potato has both high GI and GL. The GL of mixed meals can be predicted with reasonable accuracy from the GI of constituent foods.

The GI and the GL in the average diet in the USA appear to have risen in recent years due to increases in carbohydrate consumption and changes in food-processing technology.

Acute Metabolic Events Following Consumption Of A High-Glycemic Index Meal

The body has an obligatory requirement for glucose approaching 200 g/d. This is due largely to metabolic demands of the brain. Blood glucose levels are tightly regulated by homeostatic systems. [Insulin vs counter-regulatory hormones -- glucagon, epinephrine, cortisol, and growth hormone.] The rapid absorption of glucose following a high GL meal challenges these homeostatic mechanisms, complicating the transition from the post-prandial to the post-absorptive state. Within the first 2 hours of a high GL meal, blood glucose concentrations can be twice that following a low GL meal containing identical nutrients and energy. This relative hyperglycemia stimulates insulin release and inhibits glucagon release. The high insulin-to-glucagon exaggerates the normal anabolic responses (uptake of nutrients by insulin-responsive tissues, stimulation of glycogenesis and lipogenesis, and suppression of gluconeogenesis and lipolysis).

Between 2 and 4 hours after a high GL meal, nutrient absorption from the gastrointestinal tract declines, but high insulin and low glucagon levels persist. Consequently, blood glucose concentrations fall, often rapidly, to the hypoglycemic range.

About 4 to 6 hours after a *high* GL meal, low circulating concentrations of metabolic fuels trigger a counter-regulatory hormone response. This restores euglycemia by stimulating glycogenolysis and gluconeogenesis and elevates fatty acid concentrations to levels above those observed after a low GL meal.

After a *low* GL meal, hypoglycemia and its hormonal sequelae do not occur during the postprandial period due to continued absorption of nutrients from the gi tract and the rising hepatic glucose output. Thus, meals containing identical energy and nutrients can produce markedly different physiological responses.

An interesting parallel can be drawn to glucosidase inhibitors, oral agents that slow digestion of starch in the gi tract, in effect lowering the GL. (Eg, acarbose; *Precose*)¹

Postprandial hypoglycemia following consumption of *high* glycemic load foods is “so common as to be considered normal”. Postprandial hypoglycemia may be especially pronounced in obesity. The insulin-induced hypoglycemia may provoke prolonged hyperphagia and preferentially stimulate consumption of high GL foods, leading to cycles of hypoglycemia and hyperphagia.

Weight-loss efforts may exacerbate this phenomenon. A relatively severe postprandial hypoglycemia occurs after overweight subjects on very low calorie diets consume high GL carbohydrate.

Relation to diabetes:

Calorie for calorie, high GL meals result in higher blood glucose and stimulate more insulin secretion. This state of primary hyperinsulinemia may in turn cause insulin resistance. The habitual consumption of high GL meals may place the beta cells under long-term stress. Hyperglycemia itself causes impaired beta cell function (glucose toxicity); and the increased fatty acid concentrations in the late postprandial period after a high GL meal may also impair beta cell function (lipotoxicity).

Consumption of a high GL meal (compared with energy and nutrient-controlled low GL meals) adversely affects glucose tolerance at a subsequent meal.

In the management of diabetes, a low GL diet may improve management by lowering early postprandial hyperglycemia and decreasing risk of postabsorptive hypoglycemia. A number of studies found improvement in HbA1c and blood glucose levels in subjects on a low GL diets. However, recently the American Diabetes Association, citing methodological issues, concluded that there is insufficient evidence of substantial long-term benefit to recommend use of glycemic index in the management of diabetes. Other professional organizations, however, do recognize a role for GL in this regard.

Relation to Cardiovascular Disease (CVD):

Postprandial hyperglycemia had been recognized as an important risk factor for CVD, not only among persons with diabetes, but also among the general population. One study reported that the 2-hour, but not the fasting blood glucose, was independently associated with all-cause and cardiovascular mortality

(Ie, impaired glucose tolerance [post glucose load blood glucose 140 – 199] is a better risk marker for development of diabetes and cardiovascular disease than is elevated fasting glucose.)

A high GL diet may affect the risk of CVD by increasing insulin levels. Hyperinsulinemia is believed to mediate the increased risk associated with the insulin-resistance syndrome (the metabolic syndrome). The risk of developing ischemic heart disease among men age 45-76 increases by 60% for each 1-SD increase in fasting insulin.

The clinical relevance of glycemic index has been vigorously debated in recent years. The author of this article responds to the concerns about effectiveness:

1. Several dozen studies have described statistically and clinically significant improvement in end points related to obesity, diabetes, and CVD among free-living subjects on low GL vs high GL diets.
2. Observational studies link glycemic index to disease risk within prevailing dietary patterns.
3. The beneficial effect of a low GL diet may be independent of, or additive to, other dietary manipulations involving carbohydrate content or energy density.
4. Low GL diets have no known adverse effects.
5. Application of low GL diets can be simple—increase consumption of fruits, vegetables, legumes. Choose grain products processed according to traditional methods – pasta, stone-ground breads, old fashioned oatmeal. Limit intake of potatoes and concentrated sugars. This would promote diets high in fiber, micronutrients, and antioxidants, and low in energy density.

“The physician should consider this concept a practical guide.”

Conclusion:

The rate of carbohydrate absorption after a meal, as quantified by glucose load (GL), has significant effects on postprandial hormonal and metabolic responses. High GL meals produce an initial period of high blood glucose and insulin levels. This may be followed by reactive hypoglycemia, counter-regulatory hormone secretion, and elevated free fatty acid concentrations. These events may promote excessive food intake, beta cell dysfunction, dyslipidemia, and endothelial dysfunction. As a result, the risk of obesity, type 2 diabetes, and heart disease increases – “a hypothesis that derives considerable support from clinical trials and epidemiological analyses”..

Despite controversy, clinical use of GL as a qualitative guide to food selection would seem to be prudent in view of the preponderance of evidence suggesting benefit and the absence of adverse effects.

JAMA May 8, 2002; 287: 2414-23 “Special Communication” by David S Ludwig, Children’s Hospital, Boston, Mass. www.jama.com

Comment:

1 “Acarbose for Prevention of Type 2 Diabetes Mellitus” Lancet June 15, 2002; 359: 2072-77 “Acarbose could be used, either as an alternative or in addition to, changes in lifestyle to delay development of type 2 diabetes in patients with impaired glucose tolerance.”

I understand that prestigious organizations doubt the clinical applicability of the glycemic index. I abstracted this article in more detail than usual because I believe the principle of low GL is empirically reasonable. It makes common sense not to race your metabolic engine. Given that “common sense” may lead one astray, I believe that it is reasonable to believe that consistently lowering the postprandial glucose load will relieve stress on the pancreas and reduce glycation of proteins.

Gouging (eating one meal a day) is not a healthy habit. I wonder – would eating small amounts 6 times daily bring some benefits by reducing the glycemic load?

The admonition to eat fruits and vegetables, legumes, unrefined grains has been repeatedly recommended as a health-promoting intervention. I would add nuts and fish and moderate amounts of alcohol. RTJ

Ask Two Simple Questions

5-2 SCREENING FOR DEPRESSION: Recommendations and Rationale

Two articles in this issue of *Annals* summarize the current U.S. Preventive Services Task Force (**USPSTF**) recommendations for screening for depression.

The WHO identified major depression as the 4th leading cause of worldwide disease. It causes more disability than cardiovascular disease. The point estimate of prevalence is up to almost 9% among adults. Up to 50% are not recognized.

Other disabling depressive illnesses include dysthymia (chronic low-grade depression) and minor depression (an episodic, less severe illness).

Several screening instruments are available which have relatively good sensitivity. (*See text*) Simply asking two questions about depressed mood will detect a majority of depressed patients, and in some cases will perform better than the original instruments from which they were derived:

1. “Over the past 2 weeks, have you felt down, depressed, or hopeless?”
2. “Over the past 2 weeks have you felt little interest or pleasure in doing things?”

Up to 40% of positive responders will have major depression. Some “false positives” may have dysthymia of subsyndromal depressive disorders that might benefit from treatment. Others may have comorbid anxiety, panic disorder, post-traumatic stress disorder, or grief reactions. A positive screen requires further questioning.

Treatment with anti-depressant drugs is clearly effective. Psychosocial and psychotherapeutic interventions are also effective, but are more time-intensive.

Compared with usual care, screening for depression can improve outcomes, particularly when coupled with system changes that ensure adequate treatment and follow-up.

Annals Int Med May 21, 2002; 136: 760-764 “Clinical Guidelines” from the USPSTF: Recommendations and Rationale **www.annals.org**

Annals Int Med May 21, 2002; 136: 765-76 “Clinical Guidelines” from the USPSTF: A Summary of Evidence, First author Michael P Pignone, University of North Carolina, Chapel Hill.

Comment:

This presents a great responsibility and opportunity of primary care clinicians. Simply recognizing, with the patient, the presence of depression, and giving the patient opportunity to talk about it is helpful. RTJ

Medical decisions are no longer purely medical. They involve patient’s value judgments.

5-3 “WHAT SHOULD I DO DOC?”

Patients often ask their physician – “What would you do if you had my condition?”

Physicians may reply – “This is your decision to make. The right choice depends on your preferences.”

Getting patients involved in their medical decisions can often be challenging. Yet such recommendations are almost never value neutral.

This article discusses several circumstances in which physician recommendations can improve patient decision making. And help make the patient’s decisions better reflect their own preferences.

A revolution has occurred in the past 2 decades in theory and teaching about the importance of patient preferences. Medical decisions are no longer purely medical. They involve value judgments.

For example, a woman at high risk of breast cancer because of a genetic mutation may consider a prophylactic mastectomy. Whether she actually undergoes the procedure depends largely on her own preferences.

Physicians should involve patients in important medical decisions. Several methods of doing this have been suggested:

1. The “mandatory autonomous model”: Patients are required to make their own decisions. Clinicians are obligated to encourage patients to do this. Clinicians limit their role to that of being information providers only.
2. The “optional autonomy model”: Patients have the right to ignore information and cede decision-making authority. Most patients hold views consistent with this model. They prefer to receive relatively complete medical information from their clinicians while sharing decision-making authority with them. Physician recommendations would be theoretically justified because they would act on patient’s autonomous rights to cede some of their decision-making authority.

Most physicians recognize the moral justification for providing at least some patients with treatment recommendations. The recommendations have huge influence.

Conversely, some patients are so used to the paternalistic style that they are uncomfortable with any other treatment style.

Some patients are unwilling to bear the brunt of responsibility for high-stakes decisions. In the right circumstances, physician recommendations can improve medical decisions by shifting the responsibility for decisions away from families and patients.

Commission vs omission:

Does aversion to harms of commission ever cause patients to make bad decisions?

Commission: For example, some parents believe harms of vaccines outweigh benefits. People are more averse to harms of commission (eg, agreeing to giving the vaccine) than for harms of omission (not giving permission for the vaccine and taking the chance that the child will contract the disease). When looking forward, most people anticipate that they will regret commissions rather than omissions. People may overreact to harms of commissions out of a sense that they do not want to feel personally responsible for bad things that might happen as a result of decisions they make. If the child contracts the disease which might have been prevented by vaccination, it would be Mother Nature’s fault. Families may be reluctant to request a do not resuscitate (DNR) status for their loved ones out of a sense that they would somehow be contributing to their deaths. ” It is reasonable to believe that people’s fear of harms of commission unduly influences their decisions.

Omission: When people are asked to look back over their lives and state what they most regret, the majority cite omissions rather than commissions. Eg, looking back later and regretting not taking advice about a vaccine when the child developed a serious or fatal illness that could have been prevented.

There is no gold standard for determining whether health care decisions are “good or bad”, or “right or wrong”. In the right circumstances, physicians can improve patients’ medical decisions by shifting the perception of what constitutes an omission and a commission. For example: the physician, after explaining the risks and benefits of flu vaccine given to an aged father, may say, “I routinely recommend vaccination for all patients your father’s age. Is it OK if I vaccinate him?” This shifts perception of what constitutes a commission and an omission. If the daughter is passive, her father will be vaccinated. If she wants her father to go without vaccination, she must *actively* override the recommendation. Because of this recommendation, the physician will share the blame and responsibility for any ill effects. Conversely, if the daughter overrides the advice, she will feel responsible for any harms that come from failing to get the vaccine.

Discussions about do not resuscitate (**DNR**) could be improved by physician recommendations. The physician recommends DNR after discussion with the family. This shifts the definition of what constitutes an omission and a commission. The locus of responsibility has shifted more to the physician. The physician has made the DNR decision, not the family. If their loved one dies, it is the physician who decided not to resuscitate him, not the family. If the family decides against DNR and harm comes to the father, the family will feel responsible. “Families are often relieved when DNR discussions are framed as recommendations rather than open-ended questions.”

Are physician recommendations simply paternalism in sheep’s clothing?

Some physicians may feel that any new justification for physician recommendations are a step backward into the “bad old days” of paternalism. However, clinicians must recognize that even decisions to withhold a recommendation are not value neutral. If the physician declines a recommendation, she has influenced the patient’s decision. The physician has essentially told the patient that the onus is on the patient to make the decision. Yet, in many cases patients request recommendations from physicians because they are overwhelmed by the decisions they are making, and want someone else to take responsibility.

In other cases, such as that typified by a man with prostate cancer, the man must face the decision about treatment or watchful waiting. Different approaches have different outcomes, including risk of impotence and incontinence. These are very personal decisions. Physicians should not launch into a treatment recommendation without first getting a sense of what the patient’s values are.

The challenge of making physician recommendations appropriately:

In the case of a man with prostate cancer, the physician should first try to explain alternatives and probe the patient’s values. Explaining alternatives may lead patients to tell the clinician about preferences. Ultimately, even in these circumstances, when patients desire physician recommendations, physicians should feel justified in providing that recommendation. “At some point, refusals to give patient treatment recommendations are not necessarily benefiting anyone.”

It would be a mistake to return to old fashioned paternalism. Physicians need to remain aware of the very powerful role their recommendations can play in patient-choices, and the undue way their recommendations can influence patients. When physicians worry that their own interests or specialty biases are influencing their recommendations, they should encourage patients to get a second opinion. Second opinions may lead to contradictory recommendations, leaving the patient with the option of accepting one recommendation or the other, rather than feeling like they made the entire decision by themselves.

When physicians make recommendations, they should make it easy for the patient to overturn the recommendation. One simple way is to remind the patient that many other patients have made choices that go against their physician's recommendations. This does not mean a break in the doctor-patient relation. The physician can reassure the patient that he is still happy to have her as a patient.

“Ultimately, the distinction between letting patients make decisions and giving patients a treatment recommendation is often very subtle. But it still matters to patients that we relieve them of some of the stress of decision making.”

Archives Int Med May 13, 2002; 162: 977-80 Commentary by Peter A Ubel, University of Michigan, Ann Arbor.
www.archinternmed.com

Comment:

I abstracted this article in detail because decision-making affects all aspect of medical practice. Primary care clinicians deal with “all sorts and conditions” of patients and their families. Getting to know the patient as a person, listening quietly, and fostering bilateral communication, and knowing and explaining the benefits, harms, and costs of a therapy according to the best evidence are keys to helping the patient decide.

Primary care clinicians must ever be aware of the ethnic differences in the diverse populations we serve. And the patients ability to understand. RTJ

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Never too late to benefit?

5-4 ALENDRONATE IMPROVES BONE MINERAL DENSITY IN ELDERLY WOMEN WITH OSTEOPOROSIS RESIDING IN LONG-TERM CARE FACILITIES

A high percentage of elderly females residing in long-term care facilities have osteoporosis. They could benefit from interventions to increase bone mineral density (**BMD**). Most previous studies have focused on younger women.

This study examined efficacy and safety of alendronate (*Fosamax*) for treatment of elderly female residents.

Conclusion: Alendronate increased BMD in 80-year old women.

STUDY

1. Multicenter, randomized, double-blind, placebo-controlled study entered over 325 elderly women. (Mean age = 79.) All had osteoporosis.

2. Randomized to: 1) alendronate 10 mg daily, or 2) placebo.
3. All also received vitamin D (400 IU) and supplemental calcium to increase total daily intake to 1500 mg.
4. Follow-up = 2 years.

RESULTS`

1. Compared with placebo, alendronate produced significantly greater increases in BMD of the spine (+4.4%) and hip (+3.4%)
2. Also produced decreases in markers of bone turnover.
3. Adverse effects: In each group, 93% reported at least one clinical adverse experience; 33% of alendronate patients reported an upper GI adverse event vs 35% of the placebo group. Serious upper GI events were reported in 0.6% and 1.9% respectively.

DISCUSSION

1. Alendronate significantly improved BMD in both hip and spine.
2. It was generally well tolerated.
3. Women at age 65 have a life expectancy to age 84; 85-year old women have an expectancy to age 92. Thus treatment reducing fracture rate in 1 to 3 years would be appropriate. (*Note, this was not demonstrated in the study.*)
4. No bone loss occurred in the placebo group, possibly due to benefit of adequate vitamin D and calcium.
5. The new once-weekly regimen of alendronate may be particularly attractive in long-term facilities.

CONCLUSION

Alendronate increased BMD in women mean age 79.

Annals Int Med May 21, 2002; 136: 742-46 Original investigation, first author Susan L Greenspan, Beth Israel Deaconess Medical Center, Boston, Mass. www.annals.org

Comment:

Increase in BMD is an intermediate endpoint. It does not equate to clinical benefit. The important question is – does alendronate in elderly women reduce risk of fracture? It would take a much larger and longer study to establish this point. In the meantime, we might assume that increase in BMD would be associated with less risk.

Obviously, women should be started on a BMD preserving regimen at a much younger age.

All elderly women should receive vitamin D and calcium supplements. The benefit/harm-cost ratio is large.

I did not find any mention of withdrawals. Any drug associated with a 93% adverse event rate would obviously lead to withdrawals. Long-term compliance with the regimen would, in my opinion, be difficult, especially in primary care practice. RTJ

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Once a week more convenient and just as beneficial

5-5 THERAPEUTIC EQUIVALENCE OF ALENDRONATE 70 MG ONCE-WEEKLY AND ALENDRONATE 10 MG DAILY IN THE TREATMENT OF OSTEOPOROSIS

Animal studies support the rationale that once-weekly dosing with alendronate (*Fosamax*) provides similar effectiveness due to its long duration of effect on bone. It is possible that the potential of esophageal irritation may be reduced by once a week dosing.

This dosing schedule would increase convenience and compliance.

This study compared efficacy and safety of 1) once-weekly alendronate 70 mg with 2) once-weekly 35 mg, and 3) 10 mg daily in a one-year double-blind study of postmenopausal women. All had osteoporosis (bone mineral density; **BMD** of at least 2.5 standard deviations below peak pre-menopausal BMD).

Both the 70 mg and 35 mg doses were equivalent to the 10 mg daily dose. At 12 months, BMD in the lumbar spine increased by 5.1%; 5.2%; and 5.4% respectively. Increases in BMD at the hip, femoral neck, trochanter, and total body were similar.

All 3 regimens reduced biochemical markers of bone resorption.

All were well tolerated, with similar incidence of upper GI adverse effects. There was a trend toward lower incidence of esophageal events in the once-weekly regimens. (Ie, a suggestion that once-weekly dosage has the potential for improved tolerability.)

Alendronate once weekly will provide patients with a more convenient, therapeutically equivalent alternative dosing schedule.

Aging (Milano) February 2000 12(1): 1-12 Original investigation by the Alendronate Once-weekly Study Group, accessed from PubMed.

Comment:

The weekly dose of 70 mg is certainly not definitive. The PDR tends to overstate the "usual" dose of many drugs.

If, as stated in the article, 35 mg yields equivalent increases in BMD, why not use this dose? Each 70 mg tablet costs about \$17. A pill cutter will reduce cost in half. Alternatively, the 70 mg dose might be taken every 2 weeks or once a month.

The drug insert for Fosamax (*Merck*) reports:

The terminal half life of alendronate exceeds 10 years likely due to slow release from bone.

(Indeed, a recent study of an intravenous bisphosphonate zolindronic acid reported a once-yearly dose was beneficial in increasing BMD.)

The recommended dose for prevention (not treatment) is 35 mg weekly.

Adverse gastrointestinal experiences are reported to be little more than with placebo.

Cautions are repeated: Take first thing in the morning, at least one half-hour before breakfast;

(food, coffee and juice impeded absorption); take with a full glass of water and remain upright (to prevent esophagitis due to contact).

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“Don’t Be The First To Use A Newly Introduced Drug”

5-6 SAFETY OF NEWLY APPROVED DRUGS.

“Black box” warnings are frequently added to labeling of new drugs (eg, in the PDR). Removal of drugs from the market is not rare. Primary care clinicians must address the question – how hesitant should we be to prescribe new drugs? They may have unrecognized adverse effects, especially rare ones. Post-marketing trials in a few thousand (usually uncomplicated patients) do not detect all of a drug’s adverse effects. Frequent post-marketing labeling changes should be anticipated. Sometimes the new information is important enough to lead to second-line status, or to cause removal entirely. Fifty six drugs approved between 1975 and 1999 acquired black box warnings or were removed from the market. This represents 10% of the 548 new chemical entities approved.

Use of the PDR to determine warnings is convenient, but inevitably increases the delay between marketing and the warning event.

“Clearly, physicians and patients should be aware that recently marketed drugs are at risk of being found to cause unexpected serious adverse effects. But, how often do such findings affect prescribing?”

Hepatotoxicity has been the most frequent single reason for removing drugs from the market, and is still the most important reason for modification in labeling. Fortunately, the ability of drugs to inhibit hepatic metabolism and interact with other drugs is thoroughly studied. Early signs of hepatotoxicity are better assessed.¹

How reluctant should the primary care clinician be to prescribe a new drug? Certainly, by history, physicians have reason for concern about undiscovered toxicities. Even long-marketed drugs sometimes are shown to have unexpected toxicities. “There is no duration of use that allows a physician complete assurance that additional toxicity will not emerge.” But it is incorrect to describe the introduction of unsafe drugs as frequent.

Physicians contemplating prescribing a new drug should consider carefully the reason for the choice, particularly when an equally effective alternative is available. If there is sound reason to use a recently approved drug, there is no need to deny patients the treatment.

The FDA has recently proposed a rule that would include the date of approval on the package insert.

JAMA May 1, 2002; 287: 2273-75 Editorial, first author Robert J Temple, Food and Drug Administration, Rockville, MD www.jama.com

See “Timing of New Black Box Warnings and Withdrawals for Prescription Medications” JAMA May 1, 2002; 287: 2215-20 www.jama.com

Comment:

All physicians realize this. It bears repeating occasionally. The adage – “Don’t be the first to use a newly approved drug” is good advice. Wait, if possible, several years for unexpected toxicities.

If you practice long enough, you will inevitably be “caught” by sudden reports of toxicity or removal of a drug you have been prescribing for some time. It is embarrassing when a patient calls about a drug you have prescribed to report an item in the daily press which calls for caution or removal.

Beware of observational studies. They can mislead for years. Note the recent furor over adverse effects of estrogen-progestin replacement therapy. Although investigators reported beneficial effects of hormone therapy on

incidence of cardiovascular disease in post-menopausal women, they often did point out the possible role of bias (the healthy user effect). For years, many of us were convinced replacement was beneficial in reducing risk of cardiovascular disease.

1 I believe primary care clinicians are cautious about prescribing to patients with liver disease. They check for liver function more frequently when there is caution about liver toxicity. Much more is known about metabolism of drugs by the hepatic cytochrome P450 system. Beware of combining 2 drugs which inhibit the P450 system. Drug combinations can be toxic. Not only do primary care clinicians have to be concerned about potentially unknown toxicities of new drugs themselves, but must be concerned about adverse effects when added to drugs the patient is already taking. RTJ

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Selective Preventive Services Instead of Complete Physical Examination.

5-7 PUBLIC EXPECTATIONS AND ATTITUDES FOR ANNUAL PHYSICAL EXAMINATIONS AND TESTING.

Several expert panels have examined the content of, and appropriate mechanisms for providing preventive services for asymptomatic adults. One Canadian panel and four USA panels have agreed that routine annual checkups for healthy adults should be abandoned in favor of a more selective approach to preventing and detecting health problems.

This study asked -- What is the public's opinion of this?

Conclusion: Public desire for comprehensive annual physical examinations is high across the US.

STUDY

1. Population-based telephone survey in 3 US cities asked respondents to agree or disagree about -- "In addition to seeing my regular doctor when I am sick or for chronic problems, I need an annual physical examination."
2. Asked what items should be included in the annual check up.

RESULTS

1. Over 1200 responded -- 66% believed that an annual examination is necessary.
2. The great majority believed that diet, exercise, and tobacco-alcohol use should be discussed.
3. Almost all felt that BP should be measured, and heart and lungs, abdomen, reflexes, and prostate should be examined.
4. Fewer than 80% thought that hearing and vision should be tested.
5. Many tests were desired: Papanicolaou (75%); mammography (71%); cholesterol (65%); PSA (65%); urinalysis (40%); blood glucose (41%); fecal occult blood (39%); chest X-ray (36%).
6. Interest declined substantially when costs of tests were known.

DISCUSSION

1. Most adults residing in the 3 cities had a relatively high desire for an annual physical examination.
2. Over the past 3 decades, most major medical organizations have changed recommendation from a scheduled complete physical examination to selective preventive services in the context of visits for other reasons.
3. Persons who were high consumers of health services (and thus were in less need for scheduled examinations) were more likely to believe that they needed an annual examination.
4. The high expectations for specific components of an annual examination do not match current recommendations. The only blood test currently recommended by the USPSTF for screening asymptomatic adults, cholesterol, was expected only slightly more often than PSA, glucose, hemoglobin, and renal-liver-thyroid function.
5. Four tests with proven screening benefits – mammography, Pap smear, FOBT, and sigmoidoscopy – were expected less often.
6. There is need for public education about medical practices of proven and unproven benefits.
7. The survey showed a decreased desire for examination and testing when costs were presented.

CONCLUSION

The public has high expectations for a comprehensive annual physical examination and extensive routine testing. The expectations are modified by costs.

The public needs education about the value of periodic health examinations and current recommendations for specific preventive health services.

Annals Int Med May 7, 2002; 136: 652-59 Original investigation, first author Sylvia K Oboler, Denver Veterans Affairs Medical Center, Colorado. www.annals.org

An editorial by Christine Land (Annals Staff) in this issue (pp 701-03) comments:

Americans are accustomed to periodic checkups for their cars, so why not for their own bodies? Evidence suggests that the more physical and lab examinations physicians perform, the better patients feel about their health and their physician. Lab tests, even if not indicated, may help patients feel better. Some patients who do not get the tests, procedures, or referrals that they expect are less trusting of their physician and more likely to seek care elsewhere. Patients leave annual examinations, perhaps especially those that include tests, with a sense of well-being and with advice about how to foster good health until the next examination. “Annual examination is an important ritual for many.”

The fear of becoming ill and facing complex medical decisions without the benefit of a familiar physician may also motivate the public’s desire for annual examinations.

The annual exam carves out a time and place for prevention. Acute care visits leave little time for preventive care and counseling. Pediatric preventive issues are relegated to the “well baby” clinic. Why not the same for adults?

During these visits, issues related to health promotion can be addressed, instead of the visit being preoccupied by issues related to health restoration.

However, the gap between patient expectations and guideline skepticism should be narrowed. Patients should be educated about preventive practices and proven and unproven benefits.

Given that patients who receive an annual check up feel better, behave healthier, undergo more appropriate screening, and trust their physician more than those who do not undergo the examinations, skeptics need to reconsider their value.

The annual laying on of hands and stethoscope is not a needless ritual if it fosters trusting clinical relationships and ensures that patients receive effective counseling and preventive interventions.

Comment:

The blame for the public's expectations of a *complete* check-up lies with the medical community which for years enthusiastically advised the annual check up. The annual check up of the President of the US is well-publicized.

Why not me?

I believe the periodic exam is very beneficial – almost all adults have some health (usually lifestyle) risks. A brief consultation can also uncover emotional problems (depression, anxiety) as well as physical risks. The decision will depend on education, negotiation and compromise with individual patients, considering their personal preferences and understanding. RTJ

A Growing Opportunity and Responsibility for Primary Care.

5-8 TYPE 2 DIABETES IN PREGNANCY: A Growing Concern

Great strides have been made in improving outcomes of women with type 1 diabetes who become pregnant. During the past decade, type 2 diabetes (**DM-2**) in pregnancy has emerged, and is certain to become a prominent concern. We may be underestimating the true prevalence of DM-2 in pregnancy. Adverse maternal and fetal outcomes are as significant in these women as in those with type 1 diabetes.

The demographic pattern is changing, with a shift toward younger age. More women of childbearing age, more adolescents and even children are developing DM-2.

The true prevalence in pregnancy may be difficult to estimate. The figures for “pre-gestational diabetes” frequently include patients with type 1 or type 2 diabetes. Often women are assumed to have type-1 if they are taking insulin. In populations with high prevalence of diabetes, more than half the pregnant diabetic women could in fact have DM-2. In Japan, 75% of women with pre-pregnancy diabetes have DM -2. Many women with gestational diabetes are likely to have DM-2 which has previously gone undiagnosed. These women are likely to display DM-2 when tested postpartum.

A broad-based prevalence study in the USA estimated that up to 0.5% of all pregnancies were complicated with pre-gestational diabetes (type-1 or type-2) with DM-2 accounting for about 65%.

“Type-2 diabetes is being recognized as representing at least as significant a risk to both mother and baby as does type-1 diabetes.” Risks include retinopathy, nephropathy, pre-eclampsia, in the mother; and mortality, macrosomia,

neonatal hypoglycemia, and congenital anomalies in the newborn. Poor glycemic control was thought to have a major role in causing anomalies.

The rate of congenital anomalies in patients with type-1 diabetes can be reduced to that of the general population if excellent glycemic control is achieved at the time of conception. This is difficult in primary care practice. Women with type-2 diabetes in the USA are more likely to be from minority groups or immigrant populations in which cultural or socio-economic factors might prevent optimum care. It is a mistake to believe that women on diet therapy or oral hypoglycemic agents have “mild” diabetes and are therefore at less risk.

Diabetes begets diabetes. In utero exposure to diabetes leads to childhood obesity and glucose intolerance, and subsequently to diabetes in pregnancy.

Conclusion: The higher rates of type-2 diabetes in pregnancy bring with them higher rates of maternal and fetal morbidity, and might even contribute to the increasing incidence of type-2 diabetes. Better recognition of this growing entity by primary care physicians who see these patients before pregnancy, and a heightened awareness of the need for pre-pregnancy counseling about preconception glycemic control would lead to less morbidity and mortality from congenital anomalies.

Lancet May 11, 2002; 359: 1690-92 “Viewpoint”, commentary, first author Denise S Feig, Mount Siani Hospital, Toronto, Ontario, Canada. www.thelancet.com

Comment:

Primary care clinicians have the responsibility and opportunity to reduce likelihood of development of type-2 diabetes in adolescents and young women. Those at risk should be screened by post-glucose challenge (glucose intolerance; post challenge blood glucose above 140). Education and reduction of risk may avert a tragedy. RTJ

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Do Not Exclude Infected Children from School.

5-9 HEAD LICE

[*The “Clinical Practice” section of NEJM highlights a common clinical problem, presents evidence supporting various strategies for care, reviews formal guidelines (when they exist, and ends with the author’s recommendations]*

An 8-year-old girl is sent home from school after the school nurse detects head lice. She will not be permitted to return to school until the absence of lice is documented. What treatment is most likely to allow her to return to school with minimal risk to her classmates?

THE CLINICAL PROBLEM

Although *Pediculus capitis* is harmless, concern about them may cause substantial harm. Millions of school-days are lost because a “no-nit” policy excludes children who have any nits (egg cases) on inspection.

The infestation is common, endemic worldwide, and affects all ages and socio-economic backgrounds. It is more common in girls ages 5 to 11. It is rare in blacks. It is usually symptomless, and not associated with serious disease. The louse effectively infests only the human head. It feeds by sucking blood, simultaneously injecting saliva which may cause itching of the scalp. Secondary infection can occur in neglected cases.

The eggs are usually translucent and attached to a hair close to the scalp. After hatching, the 1-mm long empty egg cases (“nits”) become white and more visible. After 9 to 12 days, a grayish-dark louse becomes an adult 3-4 mm long. Nits remain firmly attached to the hair shaft, moving away from the scalp as the hair grows. Most infestations consist of fewer than 10 lice, mostly small nymphs 1 to 2 mm long.

Transmission is mainly through head-to-head contact. Lice cannot jump or fly. Pets are not vectors.

The condition is frequently misdiagnosed. Finding nits does not indicate active infection since nits may persist months after successful treatment. Diagnosis can be made by finding many eggs within a quarter of an inch of the scalp. Some authorities suggest that diagnosis should be based only on finding a living, moving louse.

A fine-toothed “nit” comb will detect more nits more successfully and quickly than visual inspection. Combing wet hair may be more effective than combing dry hair. It usually takes about one minute to find the first louse.

TREATMENT

Effective insecticides kill both lice and eggs. Experimentally, cure can be achieved in over 95% by use of topical insecticides available in the USA. (permethrin, pyrethrin, and malathion). Emergence of resistance (which has long been recognized) may decrease effectiveness.

Malathion studies reported no toxicity. Malathion is available only by prescription in the USA.

Pyrethroids are available over the counter.

Other medications, used less commonly, may have more serious adverse effects. Rare seizures, irritability have been reported associated with *Lindane* (generic; 1% shampoo).

Oral (*Stromectol*) tablets and topical ivermectin are reported to be effective. It is not licensed for this purpose. Systemic treatments are justified only with severe infestation when topical treatments are not available.

Mechanical removal of lice with wet combing is an alternative to insecticides. If all young lice (before reproducing) are removed within a few days of hatching, the infestation can be eradicated.

This method is not as effective as malathion.

Guidelines have been issued by several organizations. The CDC implies that malathion is the most effective treatment

1. Malathion: Prescription only (*Ovide*) is in an alcoholic vehicle and is flammable until dry. Currently, in the USA, malathion is the drug most likely to be effective.
2. Pyrethroids (permethrin): Over-the-counter (eg, *Nix*) . Good safety. Intermediate effectiveness
3. Wet combing: Safe. Poor effectiveness in practice.

Is exclusion from school necessary? Transmission does occur between pupils. Exclusion is almost universally practiced. However, because the infestation in a child has probably been present for weeks before detection, a few extra hours of exposure will probably make no difference in risk of transmission. “Exclusion from school based on the presence of lice or nits is not recommended by the American Public Health Association.”

CONCLUSIONS AND RECOMMENDATIONS

Parents should be informed that head lice are harmless pests that like clean hair. Infestations are common. Even doctor’s children get lice. The term “infection” should be used instead of “infestation”. Provide patients with reliable information.¹

Ideally, diagnosis should be based on the presence of a living, moving louse, best determined by fine-tooth combing.

Hair should be washed with regular shampoo to remove the insecticide at the end of the recommended application period.

The child can return to school immediately after completion of the first application of a normally effective insecticide regardless of the presence of nits. It would be useful to provide a letter of explanation to the school nurse. "Excluding children from school because of head lice results in anxiety, fear, social stigma, overtreatment, loss of education, and economic loss if parents miss work – a classic case of the cure being worse than the disease."

NEJM May 23, 2002; 346: 1645-50 "Clinical Practice" commentary by Richard J Roberts, North Wales Health Authority, Flintshire, UK www.nejm.org

1 <http://www.cdc.gov/ncidod/dpd/parasites/lice/default.htm>

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Another Suggested Benefit of Moderate Alcohol Intake.

5-10 EFFECTS OF MODERATE ALCOHOL INTAKE ON FASTING INSULIN AND GLUCOSE CONCENTRATIONS AND INSULIN SENSITIVITY IN POSTMENOPAUSAL WOMEN.

Moderate alcohol intake is cardioprotective. Hyperinsulinemia and reduced insulin sensitivity, risk factors for cardiovascular disease and type 2 diabetes, appear to be influenced by alcohol intake.

Menopause is associated with increased risk of cardiovascular disease, increased prevalence of hyperinsulinemia, and reduced insulin sensitivity.

This study evaluated whether daily consumption of low to moderate amounts of alcohol influences insulin and glucose concentrations, and insulin sensitivity in postmenopausal women.

Conclusion: Consumption of 2 drinks per day had beneficial effects on glucose metabolism.

STUDY

1. Randomized, cross-over study assigned 63 healthy postmenopausal women to consume
 - 1) 15 g/d of alcohol, or 2) 30 g/d of alcohol, or 3) an isocaloric beverage (no alcohol). Daily intake of 15 g was 5% of daily total caloric intake; 30 g was 9% of total caloric intake.
2. Total carbohydrate intake was reduced with increasing alcohol intake.
3. Energy intake adjusted to maintain constant body weight.
4. After 8 weeks in each assigned group, crossed over to the other group.

RESULTS

1. Consumption of 30 g/d, as compared with no alcohol, resulted in a reduction in fasting insulin concentration by 20%; reduction in triglycerides by 10%, and an increase in insulin sensitivity by 7%.

This was independent of body mass index.
2. Consumption of 15 g/d reduced triglycerides by 8% compared to no alcohol. Fasting insulin

and insulin sensitivity were not significantly improved statistically. However, there was a significant linear trend in reduction of insulin and increase in insulin sensitivity. (The study may have been too small to detect statistical significance of intake of 15 g.)

DISCUSSION

1. Given the source of alcohol (ethanol) and the careful control of other dietary factors and weight stability, the response can be attributed to ethanol.
2. Other studies have reported that the relative risk of developing type 2 diabetes is significantly reduced in women who consume more than 15 g alcohol (> 1 drink) per day compared with non-drinkers.
3. The observed changes in this study suggest that the moderate consumption of alcohol may increase insulin sensitivity and reduce the risk of development of type 2 diabetes and cardiovascular disease in postmenopausal women.

CONCLUSION

Consumption of 30 g/d of ethanol had beneficial effects on fasting insulin, insulin sensitivity, and triglyceride concentrations in non-diabetic postmenopausal women. This was independent of body mass index.

JAMA May 15, 2002; 287: 2559-62 Original investigation, first author Michael J Davies, US Department of Agriculture, Agricultural Research Service, Beltsville MD. www.jama.com

Comment:

Is this clinically significant? I believe the main conclusion primary care clinicians can draw is that moderate alcohol intake is not harmful metabolically and, in sensible diabetic as well as non-diabetic persons, can be enjoyed. Whether it results in lower risk of type 2 diabetes or cardiovascular disease is not known. There is one caution – obese patients with diabetes may be subject to steatosis of the liver. Even modest amounts of alcohol may exacerbate it.

TURP Associated with Fewer Adverse Effects

5-11 SEXUAL DYSFUNCTION IN MEN AFTER TREATMENT FOR LOWER URINARY TRACT SYMPTOMS

Transurethral resection of the prostate (**TURP**) is standard surgery. TURP has been reported to cause sexual dysfunction, with nearly 75% of men reporting retrograde ejaculation, and over 13% reporting impotence.

Concern about morbidity associated with TURP has led to the introduction of less invasive treatments, including laser therapy.

What is the prevalence of sexual dysfunction in men who received TURP compared with laser and conservative therapy (no active intervention)?

Conclusion: Compared with laser, TURP had a beneficial effect on aspects of sexual function.

STUDY

1. Pragmatic, randomized controlled trial entered over 300 men (mean age = 67) with lower urinary tract symptoms related to benign prostatic hyperplasia (BPH). All had been attending urology clinic. None had prostate cancer. Maximum urinary flow rate less than 15 mL/s.
2. Their lower urinary symptoms were uncomplicated.
3. Questions were asked at baseline and after intervention about erectile stiffness, ejaculatory volume, pain or discomfort on ejaculation, and whether sex life was spoiled by urinary symptoms.
4. Follow-up = 8 months.

RESULTS

1. Baseline:

Erectile and ejaculatory dysfunction were common (70%) and problematic at baseline.

And showed expected trends with ageing.

2. After treatment:

Erectile dysfunction was significantly improved after TURP.

Reduced ejaculation volume was reported in both surgery groups. It was not significantly worse in the TURP group than after laser.

Pain and discomfort on ejaculation was significantly *improved* after TURP compared with laser or non-intervention.

3. Outcomes:

	TURP (%)		Laser (%)		Conservative (%)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Erectile dysfunction	70	55	71	66	67	72
Ejaculatory dysfunction	70	83	76	86	64	73
Pain on ejaculation	17	2	18	20	19	29
Sex life spoiled	43	46	33	44	42	51

4. Among those reporting “no sexual dysfunction” at baseline:

	After TURP	After laser	Conservative
New erectile dysfunction	5%	20%	8%
Impotence	5%	8%	10%

DISCUSSION

1. This study contradicts the bulk of observational evidence that TURP causes greater sexual dysfunction than minimally invasive treatments such as laser.
2. TURP actually resulted in greater improvement in erectile dysfunction and reduction discomfort on ejaculation.
3. There were fewer cases of impotence following TURP
4. In no instance was laser significantly better than TURP.

CONCLUSION

Assertions that minimally invasive treatment such as laser therapy may have less impact on sexual function seem to be unjustified. Compared with laser, TURP had a beneficial effect on aspects of sexual function – particularly in improving erectile dysfunction and reducing pain on ejaculation.

Older men who need treatment for troublesome lower urinary tract symptoms and who wish to retain (or even improve) sexual function may consider TURP.

BMJ May 4, 2002; 324: 1059-61 Original investigation, first author Sara T Brookes, University of Bristol, UK.
www.bmj.com/cgi/content/full/324/7345/1059

An editorial in this issue comments: Compared with TURP, transurethral incision does have some advantages -- a lower incidence of complications including need for transfusion, risk of retrograde ejaculation, operative time, and length of hospital stay.

Comment:

The results of this study are provocative. Will they influence local practice? I believe primary care clinicians still rely on the experience of their consultant urologists. Opinions between urologists may differ. As usual, preferences of informed patients may tilt the decision one way or the other.

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Not effective for adults

5-12 AZITHROMYCIN FOR ACUTE BRONCHITIS

Azithromycin (*Zithromax*) is a macrolide antibiotic (the erythromycin family) commonly prescribed for acute bronchitis. It has broad spectrum of activity and infrequent adverse effects. Administration is easy (once daily for 5 days). Effectiveness in treatment of acute bronchitis is questioned.

This study compared efficacy of azithromycin with placebo (vitamin C) in treatment of acute bronchitis.

Conclusion: Azithromycin was ineffective.

STUDY

1. Randomized, double-blind study entered over 200 adults (mean age = 45) with acute bronchitis in adults. All had cough lasting over 2 days, but less than 2 weeks. None had temperature over 102⁰ or respiratory rate above 25 per minute. All had normal chest X-rays. None had evidence of underlying lung disease. (These patients were not seriously ill.)
2. Randomized to: 1) azithromycin (250 mg daily for 6 days) or 2) placebo (vitamin C).
3. Patients also received intensive symptomatic therapy. (Dextromethorphan and albuterol inhaler.)
4. Primary outcome = health-related quality of life at 7 days.

RESULTS

1. At day 7, the health-related quality of life was similar between groups; 89% of both groups had returned to their usual activities.

2. No difference in frequency of adverse events. None of the azithromycin group discontinued the drug.

DISCUSSION

1. Azithromycin was no more effective than low-dose vitamin C for treatment of acute bronchitis in adults.
It “is ineffective and should not be prescribed for patients with acute bronchitis”.
2. Exit interviews confirmed that patients did not know whether or not they received the antibiotic.

CONCLUSION

Azithromycin was no more effective than low-dose vitamin C for treatment of acute bronchitis in adults.
Lancet May 11, 2002; 359: 1648-54 Original investigation, first author Arthur T Evans, Rush Medical College,
Chicago. IL www.thelancet.com

Comment:

This is an important clinical point, given that group A streptococci have been become increasingly resistant to macrolides. COST -- \$45 for 6 -- 250 mg tablets.

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Naproxin Has Coronary-Protective Activity, But Not As Great As Aspirin.

5-13 SELECTIVE COX-2 INHIBITORS, NSAIDs, ASPIRIN, AND MYOCARDIAL INFARCTION

Concern that COX-2 inhibitors (rofecoxib; *Vioxx* and celecoxib; *Celebrex*) might predispose to thrombotic events was proposed in a study in 2000.¹ The study randomized over 8000 patients with rheumatoid arthritis to the COX-2 inhibitor, rofecoxib or the nonselective NSAID naproxin (*Naprosyn*). Aspirin was not permitted. Myocardial infarctions were more frequent in the rofecoxib group than in the naproxin group. This raised caution about the safety of COX-2. However, it was noted that naproxin inhibits production of thromboxane by 95% and platelet aggregation by 88%. Thus, the difference in outcomes may have been due to a protective effect of naproxin rather than a detrimental effect of rofecoxib. Naproxin may have coronary protective effects similar to aspirin.

A second report in 2001 also raised concern about increased cardiovascular events from COX-2 inhibitors.²

Subsequently, a review of over 28 000 patients found no excess of thrombotic events in those treated with rofecoxib vs placebo or NSAIDs other than naproxin. The risk was significantly higher in patients treated with rofecoxib than with naproxin. The investigators concluded that there was no evidence for excess cardiovascular events in patients treated with rofecoxib compared with those treated with placebo or NSAIDs other than naproxin. The difference in outcomes was likely due to an antiplatelet effect of naproxin.

This issue of *Archives* reports three studies which present evidence that patients treated with naproxin have a *decreased* incidence of myocardial infarction compared with patients receiving NSAIDs other than naproxin.

1. “Lower Risk Of Thromboembolic Cardiovascular Events With Naproxin Among Patients With Rheumatoid Arthritis” *Archives Int Med* May 27, 2002; 162: 1105-10

In this case-control study, patients with a current prescription for naproxin had a reduced risk of acute major thromboembolic cardiovascular events relative to those with no naproxin prescriptions in the past year. These results are consistent with the ability of naproxin to inhibit platelet aggregation.

2. “Nonsteroidal Anti-Inflammatory Drug Use And Acute Myocardial Infarction” Archives Int Med May 27, 2002; 162: 1099-1104

NSAIDs in general did not confer a protective effect against acute myocardial infarction. “However, use of one specific NSAID, naproxin, appeared to be associated with a reduced rate of myocardial infarction .”

3. “Association Between Naproxin Use And Protection Against Acute Myocardial Infarction” Archives Int Med May 27, 2002; 162: 1111-15

Compared with other NSAIDs, concurrent exposure to naproxin had a protective effect against acute myocardial infarction.

4. The good news for millions of NSAID users of COX-2 inhibitors is that there is no evidence that use of COX-2 inhibitors increases (or decreases) the risk of myocardial infarction.

5. The effects noted are due to the beneficial actions of naproxin, rather than a detrimental effect of COX-2 inhibitors.

6. Many users of NSAIDs and COX-2 inhibitors are in the age group at risk of coronary artery disease. Therefore, the concomitant use of low dose aspirin should be considered, especially for those with established vascular disease.³ Although naproxin reduces the risk of myocardial infarction, it offers less protection than aspirin. Low-dose aspirin should be considered in patients at risk of myocardial infarction who are taking naproxin.

CONCLUSION

Use of naproxin was associated with a reduced rate of acute myocardial infarction. There is no evidence that use of COX-2 inhibitors increases (or decreases) the risk of myocardial infarction.

The effects noted are due to the anti-platelet, anti-thrombotic actions of naproxin, rather than a detrimental effect of COX-2 inhibitors.

Archives Int Med May 27, 2002; 162: 1091-92 Editorial by James E Dalen, Editor, Archives Int Med.

www.archinternmed.com

1 “Comparison Of Upper Gastrointestinal Toxicity Of Rofecoxib And Naproxin In Patients With Rheumatoid Arthritis” NEJM 2000; 342: 152-28

2 “Risk Of Cardiovascular Events Associated With Selective COX-2 Inhibitors” :JAMA 2001; 286: 954-59

3. If aspirin is taken in addition to a COX-2, the concern is that it will negate the protective effect of the COX-2 on the stomach.

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“Cut” point = 5.5 cm

5-14 IMMEDIATE REPAIR COMPARED WITH SURVEILLANCE OF SMALL ABDOMINAL AORTIC ANEURYSMS

Because most abdominal aortic aneurysms (AAA) never rupture, elective repair is undertaken only when the risk of rupture is high. The strongest known predictor of rupture is its maximal diameter.

Whether elective surgical repair of *small* AAA improves survival remains controversial.

This study was designed to determine which of 2 strategies would result in a higher rate of survival:

1) immediate open repair, or 2) surveillance, with repair reserved for AAA that enlarge or become symptomatic.

Conclusion: Survival was not improved by elective repair of AAA smaller than 5.5 cm.

STUDY

1. Over 126 000 veterans were screened for AAA; 2% had AAA. Almost all were male.

(AAA is 4 times more frequent in males.)

2. Randomly assigned over 1100 patients age 50-79 with AAA of 4.0 to 5.4 cm in diameter to:

1) immediate open repair, or 2) surveillance (ultrasound or CT every 6 months), with repair reserved for those that became symptomatic or enlarged to 5.5 cm.

3. Follow-up mean of 5 years.

RESULTS

1. By end of follow-up:

Immediate repair group – 93% underwent repair

Surveillance group – 62% underwent repair.

2. In the surveillance group, 27% of AAA which had measured 4.0 to 4.4 cm at randomization

had been repaired at the end of the study vs 53% of those measuring 4.5 to 4.9 cm, and 81% of those measuring 5.0 to 5.4 cm.

3. The rate of death from any cause was not significantly different in the 2 groups. There was

no reduction in the rate of death related to AAA in the immediate repair group (3%) vs the surveillance group (2.6%).

4. However, the relative risk of death in the immediate group compared with the surveillance group

was 1.2. (Ie, immediate repair caused some immediate deaths. This was despite a low operative mortality of 3%.)

5. Eleven patients of 567 (2%) in the surveillance group had rupture, resulting in 7 deaths.

6. The rate of hospitalization for AAA in the surveillance group was 39% lower.

7. In 20 patients in the surveillance group repair was performed because of pain suggestive of rupture.

But no rupture was found in any patient at the time of surgery.

8. The median rate of increase in diameter in the surveillance group was 0.32 cm/y. A larger

initial diameter was predictive of increased rate of enlargement.

DISCUSSION

1. As compared with surveillance, a strategy of immediate repair did not improve the rate of survival among patients with low surgical risk who had AAA 4.0 to 5.4 cm in diameter.
2. Trends did not favor immediate repair in any prespecified subgroup defined according to age or diameter of the AAA.
3. "We did not find an increase in operative mortality or need for re-operation when elective repair was delayed until the AAA diameter reached 5.5 cm."
4. The low mortality was in part due to surgical skill and selection of low-risk patients.
5. These results are similar to a study in the UK which found no benefit from repair of AAA less than 5.5 cm.

CONCLUSION

Survival was not improved by elective repair of AAA smaller than 5.5 cm. The study supports a policy of reserving elective repair for those at least 5.5 cm in diameter.

NEJM May 9, 2002; 346: 1437-44 Original investigation, by the Aneurysm Detection and Management Veterans Affairs Cooperative Study Group, first author Frank A Lederle, VA affairs Medical Centers, Minneapolis, Minn. www.nejm.org

Comment:

If surveillance is chosen, it must be rigorous. Primary care clinicians should make absolutely sure these patients accept periodic surveillance. (Note that the great majority of those with AAA 5.0 to 5.4 cm at baseline enlarged to 5.5 cm or more in 5 years.

Medical treatment should be as rigorous as that for established coronary disease. (Indeed, many of these patients will have coronary disease.) Treatment includes: lifestyle changes (diet, weight control, and smoking cessation); lipid control; BP control; and diabetes control. Beta-blockers may have an effect of reducing rate of systolic expansion of the AAA and reducing progression. How about aspirin? I would add it in those with AAA at the low range of diameter. In those approaching 5.5 cm, the added risk of bleeding would be a consideration.

If surgery is chosen, the primary care clinician should know where to refer, choosing a center with experience and low mortality.

As usual, the individual patient's preferences must be considered. This study may give them a basis for decision-making. RTJ

Benefit in Addition to Compression Bandaging

5-15 PENTOXIFYLLINE FOR TREATMENT OF VENOUS LEG ULCERS

Most leg ulcers are venous. High compression bandaging or Unna boot is effective treatment. Despite compression, about 30% remain unhealed after a year of treatment.

Pentoxifylline (*Trental*; *Generic*) is a hemorrheological agent. It reduces the viscosity of blood by increasing flexibility of erythrocytes. It encourages migration of white cells, inhibits aggregation of platelets, and lowers viscosity of plasma. These actions might help correct microcirculatory disorders.

This systematic review quantified the effect of pentoxifylline on healing of venous leg ulcers.

Conclusion: Pentoxifylline alone, and pentoxifylline + compression was more effective.

STUDY

1. Identified 8 randomized trials (over 500 patients). Five trials compared pentoxifylline with compression vs placebo with compression. Three trials compared pentoxifylline alone with placebo.
2. Trials lasted from 8 to 24 weeks.

RESULTS

1. Pentoxifylline 1200 mg daily was more effective than placebo in healing or substantially improving ulcers.
2. Healing:

Pentoxifylline + compression	64%
Compression alone	47%
3. Substantial improvement

Pentoxifylline alone	50%
Placebo	21%
4. No more adverse events from pentoxifylline than from placebo. The most frequent adverse was mild gi upset.

DISCUSSION

1. Pentoxifylline improved healing rates compared with placebo.
2. Pentoxifylline + compression was more beneficial than pentoxifylline alone.
3. Benefits were greater in trials lasting longer than 3 months.
4. Ulcers larger than 5 cm persisting for over 6 months are unlikely to heal. This group might benefit more from pentoxifylline
5. Patients unable to tolerate compression treatment might also benefit from pentoxifylline.

CONCLUSION

These results suggest that pentoxifylline gives benefits in addition to compression for venous leg ulcers. It is possibly beneficial when used alone.

Lancet May 4, 2002; 359: 1550-54 Systematic review, first author Andrew Jull, Auckland Hospital, Auckland New Zealand. www.thelancet.com

COST—about \$50 a month for generic

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Ineffective. Intervention is necessary

5-16 HORMONAL THERAPY FOR GASTROINTESTINAL ANGIODYSPLASIA

Angiodysplasia of the intestine is a subtle and often frustrating disorder. Diagnosis may provide an explanation for repeated or obscure episodes of GI bleeding. Management is a problem, and is often unsatisfactory.

The lesions are usually small (2-5 mm in diameter) and consist of dilated mucosal capillaries draining into a tortuous, dilated submucosal vein. On endoscopy they may appear as flat or raised, single or multiple, or smooth or irregular red areas on normal mucosa. They occur most frequently in the proximal colon and cecum; less frequently in the small intestine or upper GI tract. Patients may present with iron deficiency anemia. There are no known causative or associated conditions except for age. [Cirrhosis of the liver and hereditary hemorrhagic telangiectasia (HHT; Osler-Weber-Rendu disease) may produce telangiectasia-like lesions.]

Anticoagulation therapy may make the condition manifest.

Once the lesions have begun to bleed, recurrent hemorrhage and iron deficiency anemia may develop. The anemia is resistant to iron therapy

Endoscopy and arteriography are mainstays of diagnosis. Treatment is local ablation by endoscopic techniques or surgical resection. Endoscopy with laser photocoagulation provides effective hemostasis in the great majority. Surgical resection may be required for multiple lesions.

For some years, hormonal therapy (ethinyl estradiol or norethisterone) had been used on the basis of anecdotal reports of use of these drugs in treatment of nasal bleeding in patients with HHT.) Now a randomized trial of 72 patients is reported from Spain.¹ Results were uniformly negative for a beneficial effect of hormones.

Interventional therapy is required.

Lancet May 11, 2002; 359: 1630-31 Editorial by Humphrey Hodgson, Royal Free and University College School of Medicine, London. **www.thelancet.com**

1 Gastroenterology 2001; 121: 1073-79

See illustration p 1631.

The authors state this does not rule out hormonal therapy for patients with intestinal lesions due to HHT.

Comment:

If you are a primary care clinician and practice long enough, you will encounter a patients with this disorder. As the author states, treatment of the resultant anemia with iron is ineffective. RTJ

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A new name to remember

5-17 FONDAPARINUX: A New Synthetic Pentasaccharide For Thrombosis Prevention

Almost 2 out of 3 patients undergoing major orthopedic surgery will develop post-operative deep-vein thrombosis unless prophylactic therapy is administered. During the past decade, low-molecular-weight heparin (LMWH) has emerged as the main prophylactic tool. Adjusted-dose warfarin remains an alternative. Both strategies prevent up to 80% of post-operative venous thrombotic events.

A new anticoagulant (fondaparinux) is becoming available. This synthetic compound is almost identical to the natural pentasaccharide sequence of heparin. It inhibits factor Xa.

Two studies in this issue of *Lancet* compare fondaparinux with LMWH (enoxaparin) after elective hip replacement. The primary efficacy outcome was rate of venographically confirmed deep-vein thrombosis and pulmonary embolism.

Fondaparinux appeared superior to enoxaparin:	NNT
Venous thromboembolism – 6.8% vs 13.7%	15
Proximal deep-vein thrombosis—1.3% vs 2.9%	62
Major bleeds –2.7% vs 1.7%	100 (harm)

Further experience will determine the place of fondaparinux. Will the benefits outweigh the increased risk of bleeding?

Lancet May 18, 2002; 359: 1710-11 “Commentary”, first author Henri Bounameaux, University Hospitals of Geneva, Switzerland. www.thelancet.com

Comment:

I abstracted this commentary to learn the name and the pharmacologic action of this new anticoagulant. Look for developments. I believe we will be hearing more about it. RTJ

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