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HIGHLIGHTS JANUARY 2003

1-1 WHY DO GENERAL PRACTITIONERS PRESCRIBE ANTIBIOTICS FOR SORE THROAT?

Describing the difference between "Evidence Based Medicine" and the "Real World" of practice. Despite the power of EBM, there are many instances and reasons for deviation.

1-2 ADVERSE EVENTS ASSOCIATED WITH DIETARY SUPPLEMENTS

"Dietary supplements" are associated with adverse effects that include all organ systems, age groups, and levels of severity,

Associations between adverse effects and ingredients are difficult to verify. Information systems are incomplete.

Our strong message should be:". "You do not know what you are taking". "You do not know if it is safe".

1-3 MULTIFACTORIAL INTERVENTION AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES

A targeted long-term intensive intervention aimed at multiple risk factors (hypertension, dyslipidemia, microalbuminuria) in patients with DM-2 and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50%.

1-4 GLYCEMIC EFECTS OF POSTMENOPAUSAL HORMONE THERAPY:

In women with established coronary heart disease, hormone therapy reduced the incidence of type 2 diabetes by 3.3% compared with those taking placebo. NNT (4 years to prevent one case) = 30.

And reduced incidence of diabetes by 12% in those with impaired glucose tolerance at baseline.

1-5 PREMENSTRUAL DYSPHORIC DISORDER

Selective serotonin reuptake inhibitors (SSRI) are first-line agents for PDD. Several trials have demonstrated they are superior to placebo for treatment of the emotional and physical symptoms.

Fluoxitine (*Prozac*) and Sertraline (*Zoloft*) are the most studied. A 20 mg dose of fluoxitine is as effective as the 60 mg and has fewer adverse effects and fewer dropouts. SSRIs may be given continuously or for two weeks before the expected period. Luteal phase administration has been effective.

1-6 IMPACT OF CHANGING DIAGNOSTIC CRITERIA ON INCIDENCE, MANAGEMENT, AND OUTCOME OF ACUTE MYOCARDIAL INFARCTION

Adding troponin levels as criterion for the diagnosis identified many more patients as having an acute myocardial infarction.

1-7 DIRECT-TO-CONSUMER ADVERTISING AND SHARED LIABILITY FOR PHARMACEUTICAL MANUFACTURERS

Marketing of prescription drugs has undergone substantial change facilitated by the regulatory environment governing direct-to-consumer advertising. (DTCA). Physicians who write prescriptions on the request of patients who have been influenced by DTCA, do not relinquish any of their traditional control over prescribing

1-8 ESCALATION OF DRUG USE IN EARLY-ONSET CANNABIS USERS VS CO-TWIN CONTROLS.

Associations between early cannabis use and later drug use and abuse/dependence cannot be explained solely by common predisposing genetic or environmental factors. Early initiation of cannabis (before age 17) was associated with significantly increased risk of other drug use and abuse/dependence later in life. This is consistent with early use of marijuana having a causal role as a risk factor.

Regardless of the mechanisms underlying the associations, it is apparent that young people who initiate cannabis at an early age are at heightened risk of progressing to other drug use and drug abuse/dependence.

1-9 PROPHYLACTIC TREATMENT OF MIGRAINE WITH AN ANGIOTENSIN-II RECEPTOR BLOCKER

In this study, the angiotensin II blocker, candesartan, provided effective migraine prophylaxis with tolerability comparable to that of placebo. Physicians need to be more aware of the risks associated with early use.

1-10 OBESITY AND ADULTHOOD AND ITS CONSEQUENCES FOR LIFE EXPECTANCY

Obesity in adulthood is associated with decreases in life expectancy among men, women, smokers and non-smokers. (Up to 7 years of life lost.) Combined smoking/obesity doubles risk.

1-11 PRESCRIBING ORAL CONTRACEPTIVES FOR WOMEN OLDER THAN 35 YEARS OF AGE.

OC can be safely prescribed to many women over age 35.

There are many risks and absolute contraindications. Primary care clinicians should review risks before prescribing.

1-12 PRIMARY ANGIOPLASTY VERSUS INTRAVENOUS THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION.

Primary PTCA is more effective than thrombolytic therapy for treatment of ST-elevation AMI.

1-13 ROLE OF DRINKING PATTERN AND TYPE OF ALCOHOL CONSUMED IN CORONARY HEART DISEASE IN MEN

Among men, consumption of alcohol at least 3 to 4 times per week reduced risk of MI. Neither the type of beverage, nor the proportion consumed with meals substantially altered the association.

Men who increased their alcohol consumption by a moderate amount during the follow-up had a decreased risk of MI.

1-14 OUTDATED DRUGS MAY BE USEFUL

This letter to the editor brings up an important practical point. Should we discard all drugs when they become outdated?

The correspondent believes that many drugs maintain potency long after expiration date. In developing countries and “free” clinics in the USA, the choice may be “outdated” or “none at all”.

1-15 DRUG ELUTING STENTS IN VASCULAR INTERVENTION

Immunosuppressive agents (which inhibit tumor-cell growth) may also inhibit the benign tissue proliferation characterizing intimal hyperplasia. Several immunosuppressants have been tested for potential to inhibit restenosis. Stents coated with the agents are becoming available. Local drug delivery achieves higher tissue concentrations of drugs, while producing no systemic effects. This is associated with a marked reduction in the risk of re-stenosis.

“The clinical impact of the elimination of restenosis may influence the approach to coronary artery disease, the future of cardiac surgery, and health-care economics.”

1-16 COMBINATION TREATMENT OF ANGIOTENSIN-II RECEPTOR BLOCKER AND ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR IN NON-DIABETIC RENAL DISEASE (COOPERATE)

Combined ACE-I and A II-I therapy safely retarded progression of non-diabetic renal disease more effectively than either drug alone..

1-17 OPIOID ADDICTION

In early February 2003, the SAMHSA sent a “Dear Physician” letter outlining a new, office-based approach to opioid addiction. It represents a new era in addiction treatment.

The new treatment option is based on buprenorphine, a partial opiate agonist/antagonist recently approved by the FDA. Physicians can now provide opioid addiction treatment in their own offices. It also provides access to a supportive network of treatment specialists who can address the psychosocial needs of patients undergoing detoxification or maintenance. Buprenorphine has a lower potential for abuse, a lower level of physical dependence, and weaker opioid effects than other drugs such as methadone.

The "Art" Of Medicine Deals With One Patient At A Time; The" Science" With Large Groups Of Patients.

1-1WHY DO GENERAL PRACTITIONERS PRESCRIBE ANTIBIOTICS FOR SORE THROAT?

Most sore throats are viral, self-limited, easily self-managed, and do not require antibiotics. Some clinicians continue to prescribe antibiotics for some cases. Why?

This study explored general practitioners' (**GPs**) reasons for prescribing antibiotics, and the factors that influenced their decision-making.

STUDY

1. Interviewed 40 general parishioners in the UK. Questions included opinions and beliefs about antibiotic prescribing for sore throat, management of patients, and awareness of research and policy about antibiotic prescribing, and how these influenced practice.

RESULTS

1. All GPs agreed that antibiotics are unnecessary for most patients with sore throat. They identified research, local prescribing advisers and national reports as influencing them to reduce antibiotic prescribing. Indeed, all claimed to have reduced prescribing in response to pressures to do so.
2. They estimated that they prescribed antibiotics from less than 1 in 10 to a maximum of half of patients with sore throat. Only one GP said he prescribed to half and he believed he was a high prescriber.
3. All believed that antibiotics are beneficial to some patients. Specific signs and symptoms and contexts were identified in which they would or would not prescribe antibiotics:
    Prescribed:
        If the sore throat lasts for 4 to 5 days and is getting worse.
        If the patient appears toxic. (Ie, high fever, headache, myalgia, looks "awful", and feels ill when they walk in).
        If lymph nodes are swollen, and throat looks red raw with dilated blood vessels "just like raw meat".
        If there is concern for complications.
    Do not prescribe:
        If sore throat began within 48 hours of consultation.
4. Some will tell the patient there is not strong evidence of efficacy of penicillin and give the patient the option to take or not to take the antibiotic.
5. The patient's appearance, and the duration and severity of symptoms influenced GPs about the cause and likelihood of complications. And influenced prescribing.
6. One high prescriber explained his willingness to prescribe because he had withheld antibiotics from a patient who subsequently developed septicemia. (*Individual and reported anecdotal experience are still powerful motivators.. RTJ*)
7. Other GPS said their antibiotic prescribing was influenced by previous patients.

8. Some mentioned that if patients take the trouble to consult with a sore throat, they are more likely to be ill. They probably had managed other sore throats at home before.
9. Only one GP took throat swabs when the patients appeared toxic. She found most improved while waiting for the results. However, she would prescribe if the culture grew group A streptococci, even if the patient had improved and even when she suspected the finding was probably co-incidental. No other GP experienced discomfort when prescribing under these contexts.
10. Adverse social factors lowered threshold for prescribing. (eg, poor diet and suboptimal immune function.)
11. GPs in one practice agreed to change practice policy and stopped prescribing antibiotics to all patients with sore throat. Subsequently, they saw an unprecedented rise in the number of patients with quinsy. They then returned to prescribing for severest sore throat symptoms.
12. One GP posted a notice—"Please do not ask the doctor for antibiotics as refusal often offends".
13. One GP said he formerly was very strict about not prescribing, Later he prescribed more frequently when he felt under pressure or if he was running late and it was too much to go through the detained process of saying sore throats are caused by viruses and will get better anyhow, etcetera. He also prescribed when he knew the patient would not be satisfied unless she received a prescription for antibiotic. "People aren't always as research would have them." (*An honest MD. RTJ*)
14. Delayed prescribing—giving a prescription and asking the patient not to fill it unless she got worse, or was no better in 2 to 3 days. On the whole it was regarded positively as a way to manage uncertainty, to reassure the patient, to prevent re-attendance, and to shorten the consultation. One GP said it had the potential to reduce antibiotic use, and was an indicator of patient-centered consulting. But, not all GPS used delayed prescribing.
15. GPs agreed that overuse of antibiotics would lead to development of resistance. But many were skeptical that prescribing penicillin for sore throat contributed to this significantly. "Tell me why penicillin still works in the community".
16. Prescribing antibiotics is relevant to maintaining the doctor-patient relationship, but not the most important. Patients "know that I base my advice by considering their story alongside the medical evidence. The sore throat does not exist in isolation—often I've seen the same person with blood pressure, depression, diabetes, the list goes on—so, no, my relationship with my patients isn't that fragile."
17. Communicating that the science does not support the patient's beliefs can be difficult. "If I think I am treating the whole patient and not just the virus, then I feel better about giving the antibiotic because of my holistic duty here."
18. None of the GPs interviewed described feeling very uncomfortable when prescribing antibiotics for sore throat. Most felt they had reduced their prescribing in response to external pressure to a level they felt comfortable with. Many felt there were more pressing issues.

Rationale for prescribing:

GPs did not describe appreciable discomfort in prescribing antibiotics for sore throat.

Maintaining the doctor-patient relationship was not the primary reason for prescribing. They did

not believe that withholding antibiotics greatly undermined or damaged the doctor-patient relationship.

Overall, GPs prescribed antibiotics by taking into account biomedical evidence, policy statements, and social context. But, they had difficulty in distinguishing individuals at most risk of complications.

GPs who questioned the relevance of research evidence for real life practice said that research was not conducted in comparable settings and with comparable populations.

Clinical experience and personal knowledge of their patients were other factors that led to bypassing evidence.

GPs questioned the notion that prescribing penicillin V for sore throat in the community was important as a threat to development of antibiotic resistance. Evidence accumulated in individual practices by individual GPs was given priority over research evidence.

BMJ January 18, 2003; 326: 138-41 Original investigation, first author Satinder Kumar, University of Southampton, UK www.bmj.com/cgi/content/full/326/7381/138

Comment:

I enjoyed this article. It bridges the gap between evidence-based medicine (EBM) and the real world of primary care practice. It is a good example of the value of qualitative studies.

EBM applies to populations, not to individuals. Individual patients often do not fit the inclusion and exclusion criteria of trials. I would wager that the next patient walking into your office has less than a 50% chance of strictly matching the group of patients described in meta-analysis of trials.

Even if the patient does strictly match, many factors will impede application of the evidence—cost of drugs, health illiteracy and language barriers, transportation problems, lack of family support, cognitive impairment, concurrent illness.

Indeed, many patients present problems which have not been studied and never can be studied.

Most EBM conclude with a statistical estimate—eg, the number needed to treat to benefit one patient over x time = 10.) Primary care deals with all 10. What about the 9 who do not benefit and who will needlessly endure the cost, inconvenience and adverse effects? Primary care clinicians must rely on their clinical judgment. The “art” of medicine deals with one patient at a time; the” science” with large groups of patients. RTJ

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“You do not know what you are taking”. “You do not know if it is safe”. “You are taking a great risk”.

1-2 ADVERSE EVENTS ASSOCIATED WITH DIETARY SUPPLEMENTS

“Dietary supplements”(**DS**) are not registered. Adverse effects are difficult to monitor. There is little information about their content and safety. There is cause for concern. They can cause serious adverse effects which could remain undetected.

About 20 000 DS products are on the market in the USA. Use continues to grow.

Use of products from this very diverse class of substances is intended to maintain “structure and function” of the body. This contrasts with prescription drugs which are for treatment. The burden of proof of safety has moved away from the makers of DS. The US Dietary Supplement Health and Education Act (1994) states that only dietary supplements that are “adulterated” present a “significant unreasonable risk of illness or injury”. New dietary supplement ingredients introduced after the Act could “reasonably be expected to be safe”.
However, DS do not have to undergo the mandatory prelaunch testing and post-launch surveillance which are required for prescription drugs. There is no accessible and comprehensive register of supplement names and ingredients.

Adverse events are recorded only through voluntary reporting, a weak form of surveillance. Without access to adequate information, poison control centers face obstacles in provision of services and reporting of adverse events. Centers do not always detect adverse events. Epidemiological studies are not comprehensive. A cycle exists of inadequate incoming safety information and poor outgoing reporting of new data.

This poison control center study aimed to obtain more information on adverse events associated with DS, and to assess the assumption that DS are safe and free of adulteration and are not hazardous.

Conclusion: DS are associated with adverse events of all levels of severity.

STUDY

1. Eleven poison control centers recorded details of over 1400 ingestions of DS. Of these, over 700 described symptoms.
2. Assessed the effects of multiple ingredients and long-term use and collated data for patterns of use.

RESULTS

1. Treatment of disease was the reason for use in over ¼ of reports.
2. One third of events were of greater than mild severity.
3. Both new and previously reported associations were reported:
   - Neurological (coma, seizures, cerebral bleed)
   - Cardiovascular (chest pain, conduction disturbances, arrhythmia, myocardial infarction)
   - Hematological (bleeding with raised INR comment, hepatotoxicity, increased live enzymes)
   - Metabolic (electrolyte abnormalities, metabolic acidosis)
   - Hypersensitivity (bronchospasm, angio-edema, anaphylaxis)
   - Respiratory (dyspnea, respiratory depression)
   - Genitourinary (urinary retention)
   - Death
4. Pediatric exposures were often unintentional.
5. Most products and ingredients were not identified in the information data base of the poison control centers.

DISCUSSION

1. Some persons take DS to treat disease, contrary to the avowed principle underlying their approval by the government.
2. The regulatory distinction between prescription drugs and DS may not be clear or relevant to consumers. Confusion exists between DS and prescription drugs.
3. Packaging that is not child-proof leads to unintentional ingestion of DS.
4. Serious adverse effects occurred among users of aphrodisiacs, herbal abortifacients, body builders, and among those wishing to enhance athletic performance.
5. Adulteration of products and inadvertent plant substitution may enhance inherent toxicity.
6. Severity of toxicity increased with long-term use. This contradicts the expectation that symptoms would develop only if large amounts of DS were consumed in a suicide attempt. Repeated use allows attainments of steady state pharmacokinetics (about 4 half-lives) and increases toxicity to tissues.
7. Adverse events associated with DS are most certainly under-reported.
8. "Formulation and use of multiple ingredients not only confound the establishment of cause and effect, but could cause interactive fixed supplement effects (analogous to fixed drug effects) because of the number of possible cause and effect combination is enormous."

CONCLUSION

"Dietary supplements" are associated with adverse effects that include all organ systems, age groups, and levels of severity,

Associations between adverse effects and ingredients are difficult to verify. Information systems are incomplete.

Lancet January 11, 2003; 361: 101-106 Original investigation, observational study, first author Mary E Palmer, Landspitali University Hospital, Reykjavik, Iceland. www.thelancet.com

Comment:

This data has continuing importance to primary care. We all know this. The message warrants repetition. Clinicians often have no information on what DS patients are taking, and on what the possible interactions with prescription drugs may occur. We should try to determine what DS patients are using, even though they may be reluctant to tell us.

I believe our strong message should be: "You are taking a great risk". "You do not know what you are taking". "You do not know if it is safe".

However, patients are convinced of safety of herbal mixtures based on historical use. We should point out:

There is no way we can be sure what the DS contain. The multiple ingredients vary from batch to batch. There is no way we can be sure that labeling is correct. There can be no assurance that they are safe, especially when combined with other DS or with prescription drugs. Adulteration is common.

Additional care is required to assure that children will not gain access. RTJ

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Reduced Complication Rate By 50%

1-3 MULTIFACTORIAL INTERVENTION AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES

Patients with type-2 diabetes (**DM-2**) have an increased risk of death from cardiovascular causes. The age-adjusted prevalence of coronary heart disease is twice as high as among those without diabetes. The high incidence of other macrovascular complications (stroke, peripheral vascular disease) is a major cause of illness and economic burden.

Modifiable risk factors such as hyperglycemia, hypertension, and dyslipidemia increase the risk of a poor outcome. Randomized trials thus far have focused on modifying *single* risk factors in reducing risk of both macro- and micro-vascular complications.

This study evaluated the effect of intensified, targeted, *multifactorial* interventions simultaneously aimed at several risk factors.

Conclusion: Intervention aimed at multiple risk factors reduced risk of cardiovascular and microvascular events by about 50%.

STUDY

1. Randomized, open, parallel trial entered 160 patients with DM-2 (mean age = 55). All had microalbuminuria.[1]
2. Half of the patients were randomized to conventional treatment; half to intensive treatment targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria.
3. The intensive group received behavioral (lifestyle) modifications and a stepwise introduction of pharmacologic therapy. They received individual consultations about every 3 months.
4. Interventions included:

Dietary (30% or less of fat; less than 10% saturated).

Light to moderate exercise up to 5 times weekly

Attempts at smoking cessation

Prescribed angiotensin II receptor antagonist equivalent to 50 mg captopril twice daily, irrespective of BP level.

Daily vitamin supplement.

Drug therapy:

All received low-dose aspirin

Blood glucose control: Goal = glycosylated hemoglobin < 6.5%

Oral hypoglycemic agents if Glycosylated hemoglobin remained over 6.5%:

Metformin (*Glucophage*) if overweight; gliclazide (a *sulfonylurea*) if not overweight; combination if not controlled.

Insulin (NPH) if Glycosylated hemoglobin remained over 7.0% despite maximal oral therapy. Dose adjusted on basis of morning blood glucose. If daily dose exceeded 80 U, switched to regular + NHP 2 to 4 times daily.

Hypertension: Goal = systolic < 130; diastolic < 80

All received an ACE inhibitor or an angiotensin II blocker for microalbuminuria at baseline regardless of BP.

Thiazides, calcium=blockers, and beta-blockers added if needed.

Dyslipidemia: Goal= total cholesterol < 175 mg/dL and triglycerides < 150 mg/dL

Statins usually; fibrates occasionally if triglycerides exceeded 350 mg/dL; or both.

5. Primary end point = composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stoke, revascularization, and amputation, Mean follow-up = 8 years.

RESULTS

1. Glycosylated hemoglobin, systolic and diastolic BP, total cholesterol, LDL-cholesterol, triglycerides, and urinary albumin excretion were all significantly lower in the intervention group than in controls.
2. These beneficial changes were maintained or increased over the 8 years.
3. Patients in the intervention group had a significantly lower risk of complications:

	Hazard ratio compared with controls
Cardiovascular disease	0.47
Nephropathy	0.39
Retinopathy	0.42
Autonomic neuropathy	0.37

(*All were reduced by over half. All clinically significant. RTJ*)

DISCUSSION

1. A targeted long-term intensified intervention involving multiple risk factors reduced risk of cardiovascular disease in patients with DM-2 who had microalbuminuria.
2. Five patients need to be treated for 8 years to prevent one cardiovascular event. NNT (8 y to benefit one) = 5
3. Serious adverse effects were few.
4. Could not determine which treatment component was most critical in producing the benefit.

CONCLUSION

A targeted long-term intensive intervention aimed at multiple risk factors (hypertension, dyslipidemia, microalbuminuria) in patients with DM-2 and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50%.

NEJM January 30, 2003; 348: 383-93 Original investigation, first author Peter Gaede, Steno Diabetes Center, Copenhagen, Denmark. www.nejm.org

1 Microalbuminuria is a well established independent risk factor for cardiovascular disease. The authors suggest that this group represents about 1/3 of the population of patients with DM-2

Comment:

Implementation of such a regimen is difficult and costly. The challenge for primary care is to teach and encourage these patients, and for the patients to remain enthusiastic about compliance. Not an easy task for either. RTJ

Reduced Incidence Of Diabetes By 3% To 12% In Women With Established Coronary Heart Disease.

1-4 GLYCEMIC EFECTS OF POSTMENOPAUSAL HORMONE THERAPY:

The Heart And Estrogen/Progestin Replacement Study (HERS)

Observational studies have consistently found that women taking PHT have lower fasting glucose levels and glycosylated hemoglobin levels.

This randomized study evaluated the effect of PHT on incidence of diabetes in women with established coronary heart disease (**CHD**)

Conclusion: PHT over 4 years was associated with an incidence of diabetes of 6.2% vs 9.5% in those taking placebo.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered over 2700 postmenopausal women.
   (Mean age = 67) All had a history of CHD.
2. At baseline, 26% had diabetes; 8% had impaired fasting glucose levels; 68% were normoglycemic.
3. Diabetes defined as fasting plasma glucose (**FPG**) 126 mg/dL or greater, or initiation of therapy for diabetes.
4. The 1811 women (74%) without diabetes were randomized to:
   1) Conjugated estrogen 0.625 mg + medroxyprogesterone 2.5 mg daily, or 2) Placebo.
5. Followed up = 4 years,

RESULTS

1. FPG levels increased significantly in the placebo group; did not change in the PHT group.
2. Incidence of diabetes: PHT group = 6.2%; placebo group = 9.5% [Absolute difference = 3.3%]
   (Number needed to treat to prevent one case of diabetes over 4 years = 30.)
3. Of those with impaired fasting glucose (plasma glucose 110 to 125 mg/dL) 25% assigned to PHT vs 37% of those assigned to placebo progressed to diabetes in 4 years. [Absolute difference = 12%]
   (Number needed to treat to prevent one case of diabetes over 4 years = 8.)

DISCUSSION

1. The comparative risk was lower in those taking PHT because they were less likely than the placebo patients to experience a rise in their fasting glucose over the 4 years. Women in the PHT group were more likely to maintain their glucose levels; those in the placebo group were more likely to progress.
2. Characteristics commonly associated with diabetes (eg, changes in weight or abdominal girth) were not responsible for this association in the PHT women.

3. These effects of estrogen + progestin regimens on glucose metabolism are generally consistent with results of estrogen-alone regimens.
4. Estrogens may have a beneficial effect on hepatic gluconeogenesis. (Ie, a suppression of glucose production by the liver.)
5. The study did not measure 2-hour post-prandial glucose. Thus, no effect on peripheral glucose metabolism was measured. But fewer of the group taking PHT progressed to diabetes than those in the placebo group.
6. Trials in women with type-2 diabetes have reported lower fasting glucose and glycosylated hemoglobin levels in those taking hormone therapy.
7,. The investigators comment that the patients included in the study were likely to have a higher risk of diabetes because of older age, higher body weight, and less physical activity.
8. "Postmenopausal patients at high risk of diabetes, such as those with impaired fasting glucose, may benefit from hormone therapy." But. because of the increased risk of coronary events, breast cancer, and venous thromboembolism in those taking long-term PHT, PHT is not a viable approach to diabetes prevention."

CONCLUSION

In women with established coronary heart disease, hormone therapy was associated with a reduced incidence of type 2 diabetes by 3.3% compared with those taking placebo. NNT (4 years to prevent one case) = 30.

And reduced incidence of diabetes by 12% in those with impaired glucose tolerance at baseline. NNT = 8.

Annals Int Med January 7 2003; 138: 1-9 Original investigation by the Heart and Estrogen/progestin Replacement Study (HERS), first author Alka M Kanaya, University of California, San Francisco. www.annals.org

Comment:

I am pleased to report this clinically significant outcome from PHT. It counters some of the recent adverse publicity about PHT.

The comparative adverse effects from PHT reported recently by the Woman's Health Study amounted to 19 out of 10 000 women yearly. By my calculation, the beneficial effect in reducing incidence of diabetes is 83 out of 10 000 per year.

What would benefits be in healthy women? I suspect there will be some, but not as great as in these patients with established CHD. RTJ

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Very Disturbing, But Treatable

1-5 PREMENSTRUAL DYSPHORIC DISORDER

Emotional and physical symptoms are common in the premenstrual phase of the cycle. The premenstrual syndrome (**PMS**) includes a constellation of mild-to-moderate symptoms which typically do *not* interfere with the

usual level of functioning. As many as 75% of women of reproductive age report such symptoms at some time during their lives.

Patients with premenstrual dysphoric disorder (**PDD**) experience more severe symptoms. It, by definition, is severe enough to interfere with usual social activities and relations to others. PDD affects up to 8% of women. They usually present with worsening symptoms in the mid-to-late 30s, although symptoms may have been present for a decade before. PMS and PDD are often difficult to distinguish from each other in women in their late 30s and early 40s. Symptoms continue through the menopause.

PDD is characterized by more severe symptoms than PMS: marked mood swings, depressed mood, irritability, and anxiety which may be accompanied by physical symptoms. There is substantial impairment of personal functioning, generally more in the social than in occupational domains.

These symptoms occur exclusively during the luteal phase of the cycle, with remission generally within 3 days of the onset of menses.

(*The article presents the DSM IV criteria for diagnosis on table 1 page 434)*

It is important to distinguish the marked emotional symptoms of PDD from other disorders such as major depression, dysthymia, and panic. Treatments differ. A calendar of symptoms maintained by the patient over 2 cycles demonstrating the relative absence of symptoms during the follicular phase and the substantial increase during the luteal phase is helpful.

Various treatments have been suggested:

Reducing intake of caffeine, refined sugars, and sodium.

Exercise

Vitamin B6

Calcium carbonate

Spironolactone (*Generic*)

(There are no randomized trials to confirm the benefits. But the author suggests a trial of vitamin B6 and calcium carbonate.)

Selective serotonin reuptake inhibitors (**SSRI**):

These are first-line agents for PDD. Several trials have demonstrated they are superior to placebo for treatment of the emotional and physical symptoms.

Fluoxitine (*Prozac*) and Sertraline (*Zoloft*) are the most studied. A 20 mg dose of fluoxitine is as effective as the 60 mg and has fewer adverse effects and fewer dropouts. SSRIs may be given continuously or for two weeks before the expected period. Luteal phase administration has been effective. Some data support the use of intermittent therapy.

NEJM January 30, 2003; 348: 433-38 “Clinical Practice”. review article by Tana A Grady-Weliky, University of Rochester School of Medicine, Rochester, NY www.nejm.org

COST My pharmacy quotes:

Prozac 10 mg caps $3.20 40 mg caps $4.50 (Worth splitting if possible. At 20 mg daily, cost would be $2.25)

Zoloft 25 mg $2.36 50 mg $2.36 100 mg $2.36 (Note possible savings by pill-splitting.)

More Patients Than Ever Before Now Have Myocardial Infarction.

1-6 IMPACT OF CHANGING DIAGNOSTIC CRITERIA ON INCIDENCE, MANAGEMENT, AND OUTCOME OF ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction (**AMI**) in the past was defined by criteria based on symptoms, ECG changes, concentrations of cardiac enzymes (*formerly CK-MB*) as recommended by the WHO. In 2000, the American College of Cardiology recommended changing the diagnostic criteria for AMI to include raised troponin concentrations. Troponins are more sensitive markers of myocardial damage than creatine kinase. Some patients formerly diagnosed as having an acute coronary syndrome are now considered to have an AMI.

This study investigated the impact of using the new criteria on the incidence, management, and outcome of AMI.

Conclusion: The new criteria identified many more patients as having an AMI.

STUDY

1. Followed all patients admitted with chest pain. (n = 2637). Measured Troponin T in all.
2. Identified patients with a principal diagnosis of AMI according to the old criteria.
3. Identified patients with chest pain who had raised troponin T (> 0.1 ng/mL).

RESULTS

1. The new criteria raised admissions for acute MI by 58% -- from 1671 to 2637.
2. The “new” patients were older. A higher percentage were women.
3. Thrombolysis was given to only 13 (1%) of the additional patients, compared with 40% of those who met the old criteria.
4. The additional patients had a higher 30 day mortality. This increased over one year.

DISCUSSION

1. The new criteria identified additional patients who were significantly different from those formerly classified as having AMI. The new criteria could increase admissions for AMI by about 160 000 additional cases in the UK every year.
2. Few received thrombolysis because ST segments were not raised.
3. The poorer survival may have been due in part to the older age, as well as ineligibility for thrombolysis.
4. Recent evidence suggests that these patients might benefit from early revascularization.
5. These observations have serious implications for epidemiology and treatment.

CONCLUSION

Adding troponin levels as criterion for the diagnosis identified many more patients as having an acute myocardial infarction.

BMJ January 18, 2003; 326: 134-35 Original investigation, first author J P Pell, Monklands Hospital, Airdrie, UK www.bmj.com/cgi/content/full/326/1781/911

Comment:

I believe this has implications for primary care. In some practices, clinicians must now be able to obtain troponin values immediately in order to properly triage chest pain patients. RTJ

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"It Has Not Been Established That Clinicians Have Relinquished Any Of Their Control Over Prescribing."

1-7 DIRECT-TO-CONSUMER ADVERTISING AND SHARED LIABILITY FOR PHARMACEUTICAL MANUFACTURERS

Marketing of prescription drugs has undergone substantial change facilitated by the regulatory environment governing direct-to-consumer advertising. (**DTCA**). The FDA issued new guidelines in 1997 governing DTCA. This was followed by an increase in consumer-oriented drug marketing, particularly in broadcast media. Almost all individuals in the USA have seen consumer-oriented drug advertisements.

What is the impact of DTCA on the marketplace? What is its effect on the doctor-patient relationship and public health? What are the responsibilities of physicians and drug companies related to DTCA?

Historically, under a common-law doctrine called the learned intermediate rule (**LIR**), manufacturers have been required to provide risk information only to physicians. There has been no legal duty to warn consumers directly about drug risks. The theory was that physicians, who are in a better position than consumers to understand complicated drug package inserts, would pass along the information to patients.

However, courts are now suggesting that DTCA has so fundamentally transformed physician-patient roles in prescribing decisions that the traditional justifications for the LIR no longer apply. DTCA may increase liability for drug manufacturers. The New Jersey Supreme Court recently introduced a sea change in product liability law. The court held that when drug manufacturers advertise to the public they assume a legal obligation to warn consumers directly of drug risks. The drug company involved in the suit defended itself by invoking the LIR, arguing that it had satisfied its duty to warn patients by supplying physicians (who would ultimately be responsible for prescribing the drug) with adequate risk information.

The court held that DTCA fundamentally shifted the locus of control in prescribing decisions in several ways:

> "Although the physician writes the prescription, the physician's role in deciding which prescription drug is selected has been altered by pressure from patients."
>
> Arguments about the physician's superior position for the communication of risk information no longer apply in the age of managed care, in which physicians have considerably less time to inform patients of risks and benefits.
>
> The success of DTCA belies manufacturers claim that they lack effective means to communicate directly with patients.

The court contended that the concept of patient autonomy is now so dominant that patients strongly influence which drugs get prescribed. "A decision to take a drug is not exclusively a matter of medical judgment." Consumers are taking a more active role in determining treatment choices.

Nevertheless, it has not been established that physicians have relinquished any of their traditional control over prescribing.

In the editorialist's view the key question is – Does the physician now have a much diminished role as an evaluator or decision maker? They believe that the fundamental underpinnings of the LIR should be preserved.

The editorialists comment that the net public health impact of DTCA is a function of 3 factors:

The current undertreatment of conditions that could be treated with advertised pharmaceuticals.

The amount of appropriate and inappropriate prescribing that might be stimulated by DTCA.

The amount of benefit and harm accruing to undertreated and overtreated patients.

JAMA January 22/29 2003; 289: 477-79 Editorial, first author Michelle M Mello, Harvard School of Public Health, Boston, Mass www.jama.com

Comment:

Most primary care clinicians receive requests from patients for prescriptions for a directly advertised drug. Some patients are adamant. I believe strongly that physicians cannot and should not, on any basis of time limitation or for any other reason, relinquish their *total* responsibility for the prescription and for adequately informing their patients about risks and costs as well as benefits. In some cases, the DTCA must be strongly resisted.

"DCTA" is not limited to drug companies. Family, friends, and word-of mouth or published anecdotes often lead to requests by patients for a specific drug. RTJ

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Use Of Cannabis Before Age 17 Predisposes To Later Use Of Illicit Drugs.

1-8 ESCALATION OF DRUG USE IN EARLY-ONSET CANNABIS USERS VS CO-TWIN CONTROLS.

Cannabis (marijuana) use is increasing among young people. About 1/3 of cannabis-related admissions to substance abuse programs are among persons age 12 to 17, and a further third among those age 18 to 25. A major concern of early use is the extent to which it may escalate to use of other illicit drug use and dependence. Drug dependence is best characterized as a chronic, recurring condition.

Stage theory posits that there is a sequence in which initiation and use of cannabis precedes the use of "hard" drugs such as cocaine and heroin. This theory provides a major rationale for sustaining prohibition against cannabis. Studies have suggested that early initiation of cannabis is a significant risk factor for the use of other drugs and experiencing drug related problems. Preventing or delaying early cannabis use may reduce risks of future illicit drug use.

This study used sets of twins to examine the association between early cannabis use and subsequent progression to drug abuse/dependence. Is the association between early use and later abuse influenced by inherited factors? Is it influenced by environment? Or are other factors more important?

Conclusion: The association between early use of cannabis and later drug problems *cannot* be completely explained by genetic or environmental factors.

STUDY

1. The Australian Twin Register obtained information on twins born between 1964 and 1971.
2. Conducted telephone interviews during 1996-2000 when the median age of the twins was 30. Determined whether cannabis was used before age 17. Obtained data on self-reported non-medical use of prescription sedatives, hallucinogens, cocaine/other stimulants, and opioids; and abuse or dependence on these dugs (including cannabis abuse/dependence) and alcohol dependence and tobacco use.
3. A total of 14% of the entire twin register (n = 2765 pairs) reported initiating cannabis use before age 17. Of these, 622 individuals were from same-sex twin pairs in which the twins were discordant for use of cannabis before age 17. (Ie, one used, and one did not.) 136 were monozygotic discordant twin pairs and 175 were same-sex dizygotic discordant twin pairs.

RESULTS

1. Individual twins who used cannabis by age 17 were more likely to report other drug use and drug abuse/dependence by age 30 at a rate 2 to 5 times higher than the co-twin who did not use cannabis before age 17.
2. Controlling for known risk factors (early-onset alcohol or tobacco use, parental conflict, childhood sexual abuse, conduct disorder, major depression, and social anxiety) had only negligible effects on these results.
3. The associations did not differ significantly between monozygotic and dizygotic twins.
4. The majority of subjects reporting both cannabis and other illicit drug use initiated cannabis before initiating use of other drugs.
5. Early regular use of tobacco and alcohol was also strongly associated with later illicit drug use.

DISCUSSION

1. Relative to their co-twin who had not used cannabis by age 17, the twin who had used cannabis by this age had elevated lifetime rates of other drug use, illicit drug abuse/dependence, and alcohol dependence.
2. The study provides evidence that inherited factors are not responsible for abuse. If inheritance were a major factor, one would expect that there would be little discordance between the monozygotic twins in illicit drug use. This was found not to be the case. For monozygotic discordant twins, there was no difference in the risk of the non-user twins to later use of illicit drugs than was the case for dizygotic twins.
4. The study also provides evidence that environmental factors do not play a major part in later illicit drug use. Twins raised in the same household would be expected to be highly concordant for environmental experiences. If the association between early use is explained by the environment, then a twin who did not use cannabis at an early age would be at equal risk for developing later drug-related problems as their co-twin who initiate cannabis at an early age. This was not the case.
5. Why might early use of cannabis predispose to later use of illicit drugs and alcohol?

   Exposure to cannabis may induce subtle biochemical changes that encourage drug-taking behavior.

Cannabis and heroin have similar effects on dopamine transmission.

Initial experiences with cannabis are frequently rated as pleasurable. This may encourage future use and broader experimentation.

Seemingly safe experiences with cannabis may reduce the perceived risk of, and barriers to, the use of other drugs.

Experience with, and subsequent access to, cannabis may provide access to other drugs as individuals more easily come in contact with the hard drug market.

6. The authors state, however, that it is not possible to draw strong conclusions solely on the basis of the associations shown. But, regardless of the mechanisms underlying the associations, it is apparent that young people who initiate cannabis an early age are at heightened risk of progressing to other drug use and drug abuse/dependence. Physicians need to be more aware of the risks associated with early use.

CONCLUSION

Associations between early cannabis use and later drug use and abuse/dependence cannot be explained solely by common predisposing genetic or environmental factors.

Early initiation of cannabis (before age 17) was associated with significantly increased risk of other drug use and abuse/dependence later in life. This is consistent with early use of marijuana having a *causal* role as a risk factor.

Regardless of the mechanisms underlying the associations, it is apparent that young people who initiate cannabis at an early age are at heightened risk of progressing to other drug use and drug abuse/dependence.

Physicians need to be more aware of the risks associated with early use.

JAMA January 22/29;289: 427-433 Original investigation, first author Michael T Lynsky Queensland Institute of Medical Research, Brisbane, Australia. www.jama.com

An editorial in this issue by Denise B Kandel, College of Physicians and Surgeons Columbia University, New York, expands on the study:

Regular sequences and stages of progression in which the use of alcohol and cigarettes precedes the use of marijuana, and, in turn, the use of marijuana precedes the use of other illicit drugs, has been observed in western societies. Very few individuals who have tried cocaine or heroin have not already used marijuana. The majority have also used alcohol and tobacco.

The “gateway hypothesis” implies 3 interrelated propositions -- sequencing, association of initiation, and causation:

Sequencing implies a fixed relationship between 2 substances such that one substance is initiated before the other.

Association implies that initiation of one substance increases the likelihood of initiation of a second substance.

Causation implies that the use of the first substance causes use of the second.

Causation is a controversial proposition which is widely invoked in policy debates. The preceding study addressed causation. Epidemiologists attempt to specify the role of prior drug use on the subsequent use of other drugs by controlling for confounding factors. Analyses based on this approach find that marijuana retains a significant association with subsequent use of other illicit drugs.

Comment:

This makes good common sense to me. The risk of continuing use of cannabis and the extension to other drugs is analogous to the well-established risk of continued cigarette smoking in young persons who begin to smoke during their teens. RTJ

Adding To The Drugs Already Available.

1-9 PROPHYLACTIC TREATMENT OF MIGRAINE WITH AN ANGIOTENSIN-II RECEPTOR BLOCKER

The WHO, using the Global Burden of Disease scale, rates migraine in the highest disability class.

Triptans are a major contributor to treatment of acute attacks, but only about 50% to 60% pf patients consistently respond. In many they provide only partial relief. Prophylactic treatment is indicated if patients experience frequent attacks and acute treatment alone is inadequate. .

Angiotensin-converting enzyme inhibitors (**ACE-I**) have been reported to be effective prophylactic therapy for migraine. These investigators considered that an angiotensin II receptor blocker (**A-II-RB**) might also be effective and perhaps safer because it blocks angiotensin-II at the cell level and does not interfere with bradykinin metabolism. This could reduce adverse effects such as cough and angioneurotic edema.

This study assessed a new prophylactic approach —A-II-RB therapy.

Conclusion: The A-II-RB provided effective prophylaxis.

STUDY

1. Randomized, double-blind, placebo-controlled crossover study entered 60 outpatients (age 18 to 65).
   All had frequent migraine attacks. (2 to 6 per month).
2. Randomized to: 1) candesartan cilexetil (*Atacand*), one 16-mg tablet daily, or 2) placebo for 12 weeks.
3. Then crossed over to the other group for another 12 weeks after a 4 week wash out period.

RESULTS

1. In the 12 weeks of active treatment, the mean number of days with headache was reduced from 18 to 14.

2. Outcomes over 12 weeks (means)	Candesartan	Placebo
Hours with headache	59	92
Days with migraine	10	13
Headache severity index	191	293
Level of disability	14	21
Days of sick leave	1.4	3.9

3. Adverse events were similar in both groups.
4. There was a substantial placebo effect.

DISCUSSION

1. Beta-blockers, calcium channel blockers, and ACE-I are also first-line prophylactic agents.
2. The mechanism of action of candesartan as a migraine prophylactic is not known. The main rationale for its use in this trial was the observed benefit of ACE inhibitors in other trials. Angiotensin II has several effects which may be relevant: direct vasoconstriction, increased sympathetic discharge, and increased adrenal medullary catecholamine discharge. Angiotensin II also modulates cerebral blood flow and has effects on fluid and electrolyte homeostasis, blocking both potassium channels and calcium activity in cells. It also may have an influence on dopamine and serotonin metabolism in the brain. Blocking these activities may lead to lessening of migraine attacks.
3. The adverse effects of candesartan were similar to placebo. It has no significant drug interactions. In contrast to beta-blockers, it does not affect pulse rate, and is not associated with sexual dysfunction. It can be safely used in patients with asthma. The incidence of cough is low.

CONCLUSION

In this study, candesartan provided effective migraine prophylaxis with tolerability comparable to that of placebo.

JAMA January 1 2003; 289: 65-69 Original investigation, first author Erling Tronvik, Norwegian University of Science and Technology, Trondheim. www.jama.com

Comment:

Study supported by AstraZeneca.

We now have several good prophylactic agents against migraine. The next step will be to compare them with each other, not against placebo. Until more comparisons are available, primary care clinicians must rely on trial and error individual patient-responses.

(Triptans drugs [eg. Sumatriptan; *Imitrex*] are used for treatment of acute attacks, not for prophylaxis.)

Cost is a consideration, since candesartan must be taken daily. My pharmacy quotes:

Atacand	16 mg	each tablet	$1.50
	32 mg		$2.06
Savings with a pill cutter			$0.47

Reduces Life Expectancy For Up To 7 Years. Up To 14 Years If Obese And Smoke

1-10 OBESITY AND ADULTHOOD AND ITS CONSEQUENCES FOR LIFE EXPECTANCY

Overweight and obesity are major preventable causes of premature mortality. Smoking is also a major risk.

This study, derived from the Framingham Heart Study, analyzed reductions in life expectancy and increases in premature death associated with overweight, obesity, and smoking in persons age 40 at baseline.

Conclusion: Life expectance is shortened by up to 14 years.

STUDY

1. Prospective cohort study entered over 3400 participants age 30 to 49 at baseline.
   (About half male and half female.)
2. Definitions according to BMI:

Normal weight	18.5 to 24.9
Overweight	25 to 29.9
Obese	30 or over

   (Underweight persons were not considered in the study.)
3. Determined mortality rates related to age and body mass index in over 40 years follow-up calculated according to weight at age 40.

RESULTS

1. Years-of-life lost compared to a 40 year old non-smoker; non-overweight, and non-obese:

Females	Non-smoker	Smoker
Overweight	3	
Obese	7	13
Male		
Overweight	3	
Obese	5	14

2. Mortality rates began to diverge at about 5 years after age 40.

DISCUSSION

1. The effect of obesity and overweight at age 40 on future life expectancy is striking. Among 40-year old non-smokers without previously diagnosed cardiovascular disease, overweight was associated with a decrease in life expectancy of 3 years, and obesity with a 6 to 7-year decrease. (Compared with normal weight persons at age 40.)
2. Smokers had a similar loss of years-of-life.
3. Obesity plus smoking resulted in a double burden of risk.
4. Mortality rates have improved greatly over the past 50 years. These results may now represent a relative rather than an absolute reduction in life expectancy in today's population, They are a robust estimation of the relative magnitude of lost life-years. However, obesity is much more prevalent in the USA now than 50 years ago.
6. The investigators did not make conclusions regarding any benefits made possible from weight loss.
7. The study strongly supports prevention as a first-line public health action.

CONCLUSION

Obesity in adulthood is associated with decreases in life expectancy among men, women, smokers and non-smokers. (Up to 7 years of life lost.)

Combined smoking/obesity doubles risk.

Annals Int Med January 7, 2003; 138: 24-32 Original investigation, first author Anna Peeters, Erasmus MC, Rotterdam, Netherlands. www.annals.org

Comment:

Certainly patients should be made aware of these risks. Will it influence many smokers to quit and many obese to lose weight? I doubt it. RTJ

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Despite Risks, Can Be Safely Prescribed For Many Women Over Age 35

1-11 PRESCRIBING ORAL CONTRACEPTIVES FOR WOMEN OLDER THAN 35 YEARS OF AGE.

Many women and practitioners believe that oral contraceptives (**OC**) are associated with substantial risks, especially in women over age 35. This may explain why only about 4% of women in the USA in this age group use combined OC.

Most concerns arise from earlier studies of preparations with high dose estrogen (> 50 ug of ethinyl estradiol) that were associated with substantial adverse outcomes. These findings are largely unsubstantiated by more recent studies of lower-dose formulations (< 35 ug). OC containing this dose are associated with less risk.

Risks of OC:

Hypertension: OC can increase both systolic and diastolic BPs by 4 to 9 mm Hg. BP returns to normal in 3 to 6 months after discontinuation, OC are absolutely contraindicated if BP is 160/100 or above. However, because of a greater risk of stroke and myocardial infarction, OCs should be used with caution in women with even mild increases in BP. In these patients, BP should be monitored more frequently after prescribing.

Dyslipidemia: OCs should not be prescribed for patients with LDL-cholesterol over 160, HDL-cholesterol < 35, and triglyceride > 250 until they are improved by therapy. The effect of OC depends on the estrogen dose relative to the progesterone dose. Estrogen tends to lower LDL and raise HDL (both beneficial). However it raises triglyceride levels. Progestins have the opposite effect. The favorable effects associated with the estrogen content of OC have not been linked to any reduction in cardiovascular risk.

Smoking: Smoking increases risk of death from cardiovascular disease. The risk increases as age increases. Caution in prescribing OC for women over age 35 who smoke, especially in those h=who smoke over 15 cigarettes daily. Other risk factors for cardiovascular disease should be considered for women who smoke fewer than 15 daily.

Venous thromboembolism: Estrogens increase risk for venous thromboembolism (VTE) by augmenting hepatic production of clotting factors (especially factor VII, factor X, and fibrinogen). The absolute risk for VTE is low – about 1 extra case for every 10 000 person-years of use. Age does not seem to influence thromboembolic risk.

Myocardial infarction: Increased risk of myocardial infarction has been reported in women who take OC and smoke. Also in women with hypertension, diabetes, and dyslipidemia who take OC.

Ischemic stroke: An increased risk of ischemic stroke has also been reported, although women taking less than 35 ug and who are older than 35 had no increase in risk as long as their BP was checked before onset. Two major studies found no increase in risk of stroke among women taking less than 35 ug, even in smokers and in those over age 35. By contrast, a recent meta-analysis reported increased risk of stroke in those taking less than 50 ug.

Migraine with aura: Also associated with increased risk of ischemic stroke. OC use has been reported to increase risk. The WHO recommends that women over age 35 who have migraine should not take OC. And in those of any age who have focal neurological signs with their migraine.

Breast cancer: The relation between OC and breast cancer (**BC**) has been controversial. Some studies report no increased risk, or only slightly increased risk. A Collaborative Study reported an increased risk on those currently taking OC. Risk declined as time from discontinuation increased. It is widely recommended that women with a first-degree family history of BC should not take OC.

Benefits of OC:

Prevention of pregnancy: Many pregnancies in women over age 35 unintended.

Ovarian cancer prevention: OC clearly reduce risk of ovarian cancer.

Relief of peri-menopausal symptoms: OC relieves most symptoms associated with the peri-menopause (hot flashes, mood swings, insomnia, menstrual irregularity, vaginal dryness). Standard OCs are 4 to 10 times more potent than hormone replacement therapy. HRT does not reliably prevent pregnancy.

Acne: Acne is still common among older women. OC have been reported to reduce severity of acne by their ability to reduce free testosterone levels through an increase in sex-hormone binding globulin. They also reduce hirsutism and decrease menstrual bleeding in women with polycystic ovarian syndrome.

Bone mineral density: Some studies have reported an increase in bone mineral density associated with OC. However, data conflict.

Which OC to select? One with the lowest estrogen dose. Those containing 20 ug of estrogen do not seem to exhibit adverse coagulation effects. Cardiovascular risk is clearly reduced in those containing less than 35 ug. There is no evidence that the type of progestin affects risk of stroke or myocardial infarction.

Side effects: About 25% experience minor side effects, most commonly during the first 3 months. Abnormal bleeding is the most common cause of discontinuation. Nausea, weight gain, mood changes, breast tenderness, and headache also occur. Low dose estrogen may reduce likelihood of many bothersome effects.

Check before prescribing: Pelvic examinations are no longer recommended as necessary.

Checking after prescribing: Annual follow ups are usual. If BP seems a problem, check every 2 to 3 months.

Breakthrough bleeding: Occurs in up to 30% in the first month. It typically resolves after a few cycles. Women should be encouraged to continue. Smoking may increase likelihood of bleeding. Switching to another preparation may reduce likelihood. NSAIDs may alleviate bleeding.

Conception has been reported as late as age 56. It is important to ensure that OC is no longer necessary. If hormone replacement therapy is desired, it is recommended at age 50.

Conclusion: OC can be safely prescribed to many women over age 35.

Annals Int Med January 7, 2003;138: 54-64 Review, first author Christine Seibert, University of Wisconsin, Madison www.annals.org

Check list: WHO absolute contraindications to OC (Unacceptable risk)

Postpartum up to 6 weeks and breastfeeding
Age over 35 and heavy smoker
Systolic BP over 160 and diastolic 100 or over
Hypertension with vascular disease
Diabetes with micro- or macro vascular disease
History of deep vein thrombosis or pulmonary embolism
Major surgery with immobilization
History of ischemic heart disease
Severe headaches with focal neurological signs
Current breast cancer
Hepatitis, cirrhosis

Comment:

Despite the long list of risks, pregnancy would be associated with even greater risk
Primary care clinicians should review contraindications before each prescription.
We should prescribe the lowest dose estrogen.
Dangers of hypertensions and smoking should be stressed. RTJ

Primary Angioplasty Wins

1-12 PRIMARY ANGIOPLASTY VERSUS INTRAVENOUS THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION.

Many trials have compared *primary* percutaneous transluminal coronary angioplasty (**PTCA**) with thrombolytic therapy for acute myocardial infarction (**AMI**). This study combined results of randomized trials to ascertain which reperfusion therapy is most effective.

Conclusion: PTCA is more effective.

STUDY

1. Systematic search identified 23 randomized trials which together assigned over 7700 patients.
   All had acute ST elevation MI.
2. Patients were randomized to: 1) *primary* PTCA or 2) thrombolysis. Primary PTCA is not accompanied

by thrombolysis.

3. Some patients received streptokinase; most received accelerated tissue plasminogen activator (t-PA).
4. Stents were used in 12 trials; glycoprotein IIb/IIIa inhibitors in 8.
5. Some patients were transferred to primary PTCA sites from sites that could not perform PTCA.

RESULTS

1. Primary PTCA was more effective than thrombolytic therapy:

	Primary PTCA (%)	Thrombolysis (%)	
Short-term death	7	9	
Non-fatal reinfarction	3	7	
Stroke	1	2	
Combined death, non-fatal MI, stroke	8	14	(NNT = 17)
Major bleed	7	5	

2. Benefits of PTCA were independent of the type of thrombolytic therapy.
3. Benefits of PTCA were maintained in patients who were transferred for primary PTCA.
4. Benefits of PTCA remained during long-term follow-up.

DISCUSSION

1. These findings indicate that primary PTCA is better than thrombolytic therapy at reducing short-term major adverse cardiac events in patients with ST elevation AMI.
2. The favorable results were sustained during long-term follow up. (6 months.)
3. Favorable results were maintained even when reperfusion was delayed because of transfer to another center for primary PTCA as compared with on-site thrombolysis.
4. More recent trials addressed important questions with respect to safety and efficacy of emergent hospital transfer for primary PTCA and for PTCA done in hospitals without surgical backup.
5. Variation in individual operator experience and hospital volume of primary PTCA implies that this procedure is applicable to a wide range of hospitals. However, the favorable results from PTCA are applicable only to hospitals with well-established primary PTCA programs, and dedicated and experienced teams of operators.
6. Bleeding complications were more common in the PTCA groups. Most bleeding was localized to the access site. Now, with use of lower doses of heparin, smaller sheath sizes, and improved operator technique, the rate of bleeding complications will decrease.
7. What about the longer delay in transferring patients to the catheterization laboratory? Previous studies reported that, despite delay, outcomes were more favorable in the PTCA groups.

CONCLUSION

Primary PTCA is more effective than thrombolytic therapy for treatment of ST-elevation AMI.

Lancet January 4, 2003; 361: 13-20 Quantitative review of randomized trials, first Author Ellen C Keeley, University of Texas Southwestern Medical Center, Dallas www.thelancet.com

Comment:

There have been many reports comparing primary PTCA with thrombolysis over the years. This study establishes primary PTCA as the best treatment option. This however, pertains only to centers with expert interventional cardiologists. And when access is reasonably prompt.

Coated stents will improve efficacy of PTCA.

Primary care clinicians must know the availability of primary PTCA in order to promptly refer patients with chest pain.

Another problem has arisen. More patients are being diagnosed as having AMI without ST-elevation. Many patients who were formerly diagnosed as having unstable angina are now considered to have acute myocardial infarction on the basis of troponin determinations. Troponins have higher sensitivity than CK-MB. Primary PTCA may also be beneficial in these patients. RTJ

Light To Moderate Alcohol Consumption Reduces Risk Type Of Alcohol Not Important.

1-13 ROLE OF DRINKING PATTERN AND TYPE OF ALCOHOL CONSUMED IN CORONARY HEART DISEASE IN MEN

Moderate drinking confers a decreased risk of myocardial infarction (**MI**). This study asks – What is the role of the drinking pattern and type of beverage?

Conclusion: Consumption of alcohol at least 3 to 4 days per week was inversely associated with the risk of MI. Neither the type of alcohol nor consumption with meals substantially altered the protective effect.

STUDY

1. Assessed the association of alcohol consumption with risk of MI in over 38 000 male health professionals, age 40 to 75 at baseline. All were free of cardiovascular disease at baseline.
2. Determined consumption of beer, red wine, white wine, and liquor every 4 years by questionnaire.
   Standardized portions; one can of beer; one 4 oz glass of wine; one shot of liquor.
   Considered ethanol content to be 12.8 g for beer; 11 g for wine; 14 g for liquor.
   Categorized average daily alcohol intake in grams into 7 categories: 0.1 to 4.9; 5 to 9.9; 10 to 14.9; 15 to 29.9; 30 to 49.9; and 50 or more
3. At baseline, increasing alcohol consumption was positively associated with smoking, hypertension, and hypercholesterolemia.
4. Documented cases of non-fatal MI and fatal coronary disease over 12 years. Related incidence with amount of alcohol consumed.

RESULTS

1. During 12 years follow-up there were 1418 cases of MI. A graded, inverse relation between alcohol and risk of MI was observed. As compared with men who consumed alcohol less than once a week, men who consumed alcohol 3 to 4, or 5 to 7 days per week had decreased risk. (Relative risks = 0.68 and 0.63.)
2. Risk was similar between very light drinkers (0.1 to 5 g daily) and abstainers. (*Ie, no protective effect.)*
3. The risk reduction was similar among those who consumed 10 g alcohol per drinking day and those who consumed 30 g or more.
4. Alcohol consumption was also inversely associated with risk of undergoing a coronary revascularization procedure. Lowest risk was among those who consumed 50 g or more daily. (RR =0.59)
5. More frequent use (3 or more drinks per week) was associated with lower risk compared with use on fewer than 3 days per week. (RR between 0.66 and 0.77 varying with amount drunk.)
6. The inverse association was evident in all decades of life.
7. Use of aspirin, body mass index, exercise, blood pressure, diabetes, family history, did not modify the association.
8. No single type of beverage conferred additional benefit.
9. Consumption with meals conferred no additional benefit.
10. For men who increased their intake by 10 g during the follow-up period, the relative risk of MI decreased to 0.55 compared with those who did not increase their intake.

DISCUSSSION

1. Alcohol consumption was consistently associated with a lower risk of coronary heart disease, regardless of the type of beverage, the proportion consumed with meals, or the type of coronary outcome.
2. The drinking pattern had an important effect, with a lower relative risk among men who consumed alcohol 3 or more days per week, even if the amount consumed per drinking day was small to moderate.
3. Episodic consumption of large amounts of alcohol (binge drinking) has been associated with a high risk of coronary heart disease.
4. The results of this study emphasize that the frequency of alcohol consumption is the primary determinant of the inverse association.
5. Although there was a decreased risk among frequent drinkers age 40-50, the absolute benefits of moderate drinking will be most apparent in older adults because they are at increased risk of coronary heart disease.

CONCLUSION

Among men, consumption of alcohol at least 3 to 4 times per week was inversely associated with the risk of MI.

Neither the type of beverage, nor the proportion consumed with meals substantially altered the association.

Men who increased their alcohol consumption by a moderate amount during the follow-up had a decreased risk of MI.

NEJM January 9, 2003; 348: 109-118 Original investigation, first author Kenneth J Mukamal, Beth Israel Deaconess Medical Center, Boston, Mass. www.nejm.org

Comment:

Many studies have reported a protective effect of alcohol, so much so that some authorities consider abstinence from alcohol to be a risk factor. There is a J shaped curve. Heavy drinking and binge drinking are associated with increased risk.

The bottom line is — drink moderately and frequently.

It is interesting that moderate alcohol intake apparently reduced the adverse effects of other risk factors. (eg, obesity, lack of exercise, diabetes, dyslipidemia) Also of interest -- apparently as patients age, moderately increasing or beginning alcohol consumption lessens risk.

How should the primary care clinician respond? I believe the one-a-day drink (and only one drink) rule would be a reasonable recommendation to very select patients. For those who already drink, advice to drink a moderate amount daily would be appropriate, rather than advice to drink more heavily on weekends. According to this study, drinking on week ends conferred no protection.

For those who do not drink, and have no objection to drinking, this evidence may be provided to the subset of patients who are emotionally stable, letting the individual patient decide.

Does combined low-dose aspirin + moderate alcohol provide additional protection? The answer to this is not known. The study found no benefit from aspirin in the moderate drinkers. RTJ

"Outdated, Or None At All"

1-14 OUTDATED DRUGS MAY BE USEFUL

Some commentators suggest that out-of-date drugs donated to poor countries should be discarded.

This correspondent disagrees. Often in situations in developing countries, the alternative to outdated medicine is no medicine at all. He has used lidocaine which was still effective 10 years after expiration. Very outdated tamezepam was effective in helping him sleep.

The issue of out-of-date drugs and medical devices is an extremely sensitive one with customs officials in developing countries. Those without scientific training who see a label stating that the drug has expired may feel responsible to destroy or confiscate it to protect the country from the condescending benevolence of the rich Western world.

The reality is that medicines do not expire. Like old soldiers, they just fade away, usually very, very slowly. It would be better if medicines were instead labeled –"after XX date, this drug can no longer be guaranteed to be 100% effective, especially if it has been stored in hot or very light conditions."

BMJ January 4, 2003; 326: 51 Letter to editor from John Sandford-Smith, Leicester, UK
www.bmj.com/cgi/content/full/326/7379/51

Comment:

I abstracted this letter because it pertains to the practice of medicine in “free” clinics in the USA. Drug companies and individuals are generous in donating drugs. Inevitably some become out of date. Attending clinicians then may have the decision to use the “outdated” drug, or write a prescription. In many instances the prescription cannot be filled because the patient lacks funds or transport to a pharmacy. As the correspondent states, the choice is then “outdated” or “none at all”.

I believe clinicians attending these clinics often dispense out-of-date drugs. Drugs obviously do not lose all potency at midnight the day of expiration. Clinical judgment can and must be used. RTJ

“May Influence The Approach To Coronary Artery Disease, The Future Of Cardiac Surgery, And Health-Care Economics.”

1-15 DRUG ELUTING STENTS IN VASCULAR INTERVENTION

Restenosis is the most important long-term limitation of stent implantation for coronary artery disease. In-stent restenosis is a refractory coronary lesion which results from neointimal hyperplasia. Angioplasty causes endothelial denudation and exposes subintimal components resulting in platelet adherence and aggregation, fibrinogen binding, and thrombus formation. In contrast, after the vascular injury caused by stents, the key mechanisms for restenosis are growth and migration of vascular smooth muscle cells. This results in neointimal proliferation. In contrast to the restenosis after balloon angioplasty, restenosis after stent placement consists of extracellular matrix and collagen, with less cellular infiltration.

Immunosuppressive agents (which inhibit tumor-cell growth) may also inhibit the benign tissue proliferation characterizing intimal hyperplasia. Several immunosuppressants have been tested for potential to inhibit restenosis. Stents coated with the agents are becoming available. Local drug delivery achieves higher tissue concentrations of drugs, while producing no systemic effects.

Sirolimus is an immunosuppressant and antimitotic agent. It has been used as an anti-rejection agent in renal transplant patients. It blocks expression of inflammatory cytokines and inhibits cellular proliferation. A recent randomized trial of sirolimus coated stents vs uncoated stents in over 200 patients, reported zero occurrence of 50% of more restenosis at 6 months vs a 27% occurrence with uncoated stents. This offers hope for the elimination of in-stent intimal hyperplasia.

Other stent-coating agents are being investigated.

“The clinical impact of the elimination of restenosis may influence the approach to coronary artery disease, the future of cardiac surgery, and health-care economics.”

Lancet January 18, 2003; 361: 247-49 “Rapid Review”, commentary, first author Rosella Fattori, University Hospital S Orsola, Bologna, Italy.

Comment:

While not directly relevant to primary care, we should be aware of these developments and their application by our cardiologist consultants. RTJ

Two Drugs Better Than Either One Alone

1- 16 COMBINATION TREATMENT OF ANGIOTENSIN-II RECEPTOR BLOCKER AND ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR IN NON-DIABETIC RENAL DISEASE (COOPERATE)

In Japan, end-stage renal disease (including non-diabetic disease) is common. Halting progression of non-diabetic renal disease (**NDRD**) is an essential goal.

The renin-angiotensin-aldosterone system (**RAAS)** has an important role in progression of NDRD. Angiotensin-converting enzyme inhibitors (**ACE-I**) are more effective than other anti-hypertension drugs in delaying progression. However, about 20% of patients who are treated with ACE-I progress to an end-point of doubling baseline creatinine or end-stage renal disease at 3 years. ACE-I produces highly variable reductions in proteinuria.

Since ACE-I often fails to prevent progression, the investigators compared efficacy and safety of combined ACE-I + angiotensin II inhibitor (**A-II-I**) with ACE-I alone and with A-II-I alone.

Conclusion: The combination was more effective than either alone, and was safe.

STUDY

1. Randomized-controlled study entered 301 patients with NDRD. During a run in period, 38 were excluded, mainly for dry cough. 256 followed to completion. .
   - Almost all had hypertension.
   - Glomerular disease (IgA nephropathy, focal segmental sclerosis, membranous proliferative glomerulonephritis) was the most common causes. Some had hypertensive renal disease, some polycystic disease.
   - Mean glomerular filtration rate at baseline = 38 mL/min; urinary protein 2.5 g/d.
2. Randomized to:
   1) Losartan 100 mg daily (A II-I)
   2) Trandolapril 3 mg daily (ACE-I)
   3) Both in equivalent doses.

   (Doses were gradually increased to these levels.)
3. Primary endpoint = doubling of serum creatinine or end-point renal disease.
4. Follow-up = 3 years.

RESULTS

1. Outcomes:	Losartan	Trandolapril	Both
Reached combined endpoint at 3 years:	23%	23%	11%

2. Only one patient in the combined group required dialysis vs 3 and 7 in the other groups.
3. Blood pressure response was similar between groups (to a mean 128/80).

4. The combined drugs produced a greater fall in urinary protein excretion:

Losartan	- 42%
Trandolapril	- 44%
Both	- 76% (From about 2.5.g /d to about 0.6 g/d)

5. In the small group with nephrosclerosis benefits were less evident.
6. Adverse effects were similar between groups. No serious adverse reactions were reported even in patients with advanced renal disease.

DISCUSSION

1. In non-diabetic patients with moderately reduced renal function and moderate daily protein excretion, the combination of drugs was significantly better in producing renal survival than either drug alone.
2. Proteinuria has been shown to have a causal role in progression of renal dysfunction in various renal diseases. The most striking difference between groups was the antiproteinuric effect of the combined drug group. "The 3-year renal survival is mainly attributable to this effect." The antiproteinuric effect in the combined drug group was more evident in those with higher baseline excretion.
3. This study lends support to the theory that the RAAS system has a role in progression of renal disease.
4. Even with maximum doses of two drugs, many patients progressed to end-stage disease. Further strategies are required to improve prognosis.

CONCLUSION

Combined ACE-I and A II-I therapy safely retarded progression of non-diabetic renal disease more effectively than either drug alone..

Lancet, December 17, 2002; First author Naoyuki Nakao, Showa University, Japan

Http://image.thelancet.com/extras/01art11215web.pdf

Comment:

Will these benefits also be evident in diabetic renal disease? I believe so.

As the investigators commented, these results may not apply to all subsets of patients with NDRD. RTJ

Office-based Treatment --A Breakthrough

1-17 OPIOID ADDICTION

(*Letter To Physicians From the Substance Abuse and Mental Health Services Administration (SAMHSA) of the Department Of Health And Human Services*)

In early February 2003, the SAMHSA sent a "Dear Physician" letter outlining a new, office-based approach to opioid addiction. It represents a new era in addiction treatment.

The new treatment option is based on buprenorphine, a partial opiate agonist/antagonist recently approved by the FDA. Physicians can now provide opioid addiction treatment in their own offices. It also provides access to a supportive network of treatment specialists who can address the psychosocial needs of patients undergoing detoxification or maintenance. Buprenorphine has a lower potential for abuse, a lower level of physical dependence, and weaker opioid effects than other drugs such as methadone.

Two forms of the newly approved drug are available for sublingual use: *Subrex* (buprenorphine) and *Suboxone* (buprenorphine + naloxone). Clinical guidelines, when completed, will be available at www.buprenorphine.samhsa.gov.

Opioid addiction is a major social and public health problem. Only about 25% of the nearly one million heroin addicts in the US receive medical treatment. The new strategy will encourage addicted persons to seek treatment and remain in treatment.

Physicians seeking to dispense or prescribe these drugs must obtain a waiver. SAMHSA is supporting the required medical education in order to qualify.

Letter to USA Physicians February 2003 from Charles G Curie, and H Wesley Clark, Substance Abuse and Mental Health Services Administration. Rockville, MD.

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