

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS
SEPTEMBER 1999

SPIRONOLACTONE TREATMENT FOR SEVERE HEART FAILURE

ALDOSTERONE AND SPIRONOLACTONE IN HEART FAILURE

ZANAMIVIR FOR INFLUENZA: A Public Health Perspective

USE OF THE ORAL NEURAMINIDASE INHIBITOR OSELTAMIVIR IN INFLUENZA

BRITISH HYPERTENSION SOCIETY GUIDELINES FOR HYPERTENSION MANAGEMENT

ADVERSE EFFECTS OF ALCOHOL IN YOUNG MEN

FUNCTIONAL FOODS

COMPUTED TOMOGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF APPENDICITIS

FUNCTIONAL SOMATIC SYNDROMES: One or Many?

GUIDELINES FOR HEALTHY WEIGHT

HOMOCYSTEINE IN HEALTH AND DISEASE

HOME MADE SPACERS FOR BRONCHODILATOR THERAPY IN CHILDREN WITH ASTHMA

DIGOXIN IN THE TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION

CAN IT WORK? DOES IT WORK? IS IT WORTH IT?

SURROGATE MARKERS ADEQUATE TO ASSESS CARDIOVASCULAR DISEASE DRUGS?

PATERNALISM OR PARTNERSHIP?

INSTILLING PROFESSIONALISM IN MEDICAL EDUCATION

GAINING INFORMED CONSENT FOR SCREENING

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HIGHLIGHTS SEPTEMBER 1999

9-1 THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

Blockade of aldosterone receptors by spironolactone, in addition to standard therapy with ACE inhibitors, loop diuretics, and digoxin substantially reduced risk of both morbidity and mortality among patients with severe HF. NEJM September 2, 1999; 341: 709-17

9-2 ALDOSTERONE AND SPIRONOLACTONE IN HEART FAILURE

The study indicates that the beneficial effects of spironolactone in blocking aldosterone receptors are additive to those of ACE inhibitors. This is an important therapeutic advance. Therapy of HF should be broadened to include spironolactone as long as renal function is adequate. NEJM September 2, 1999; 341: 753-54

9-3 ZANAMIVIR FOR INFLUENZA: A Public Health Perspective

It is effective in preventing clinical influenza in healthy adults by about 66%. If infection occurs, the drug reduces duration of major symptoms by several days, and lowers complications of bronchitis and pneumonia, as well as use of antibiotics.

But, "No clear evidence exists for its safety and efficacy in patients with serious respiratory or cardiac disease as these patients have been excluded from clinical trials." BMJ September 11, 1999; 319: 655-56

9-4 USE OF THE ORAL NEURAMINIDASE INHIBITOR OSELTAMIVIR IN EXPERIMENTAL HUMAN INFLUENZA

Prophylaxis and early treatment with oral oseltamivir were both associated with significant antiviral and clinical effects in experimental human influenza. JAMA October 6, 1999; 282: 1240-46

9-5 BRITISH HYPERTENSION SOCIETY GUIDELINES FOR HYPERTENSION MANAGEMENT 1999: Summary

This article summarizes guidelines for management of hypertension. Since previous British guidelines (1989 and 1993), new evidence has emerged on optimal BP targets; management of hypertension in diabetic persons; treatment of isolated systolic hypertension; comparison of the antihypertensive efficacy and tolerability of different drug classes; the role of non-pharmacological measures for prevention and treatment of hypertension; and additional benefits associated with the use of aspirin and statins. BMJ September 4, 1999; 319: 630-35

9-6 ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND MORTALITY, MYOCARDIAL INFARCTION, AND STROKE IN 25 YEAR FOLLOW UP OF 49 618 YOUNG SWEDISH MEN

Alcohol clearly had a negative net effect on health up to age 45. This supports a restrictive alcohol policy with recommendations for little or no alcohol consumption by young men. BMJ September 25, 1999; 319: 821-22

9-7 FUNCTIONAL FOODS

"Functional food' has become a buzz word both in nutrition research and the food industry. The term hints of a future in which specially developed foods will protect consumers from a variety of diseases and discomforts. How realistic is this expectation?" Lancet September 4, 1999; 354: 794

9-8 ULTRASONOGRAPHY AND LIMITED COMPUTED TOMOGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF APPENDICITIS

CT following a negative or indeterminate ultrasound was highly accurate in the diagnosis of appendicitis.

9-9 FUNCTIONAL SOMATIC SYNDROMES: One or Many?

This article reviews the concept and importance of somatic symptoms and syndromes. On the basis of a literature review, the authors conclude that a substantial overlap exists between the individual syndromes, and that similarities between them outweigh the differences. Many patients with different functional syndromes also share non-symptom characteristics. Similarities are apparent in case definition, reported symptoms, and in non-symptom associations such as patients' sex, outlook, and response to treatment. *Lancet* September 11, 1999; 354: 963-39

9-10 GUIDELINES FOR HEALTHY WEIGHT

BMI 19 to 25; waist circumference 40 inches in men, 35 in women; no more than 10 pound weight gain after age 21. Even small gains in weight within the range of healthy weights can carry health risks. Physicians should counsel their adult patients to make small but permanent adjustments in physical activity and eating patterns if they approach the upper limit of the range for healthy weight. *NEJM* August 5, 1999; 427-34

9-11 HOMOCYSTEINE IN HEALTH AND DISEASE

The epidemiological evidence connecting risk with elevated levels is consistent, strong, and biologically plausible. The risk is also independent of other risk factors. ² But data from prospective studies are weaker, with some conflicting results. Causality has not been proven. *Annals Int Med* September 7, 1999; 131: 387-88

9-12 HOME MADE SPACERS FOR BRONCHODILATOR THERAPY IN CHILDREN WITH ACUTE ASTHMA

A 500 mL plastic bottle is an effective alternative to a conventional spacer. It may be a valuable application in developing countries. *Lancet* September 18, 1999; 354: 979-82

9-13 DIGOXIN IN THE TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION

1. In the absence of HF, digoxin has no effect on the conversion rate of AF of recent (< 7 days) onset.
 2. Digoxin has a significant, albeit clinically modest, effect on reducing mean ventricular rate in symptomatic attacks. (Eg, reduction to 125 beats/min compared with 138 for placebo.) However, digoxin does not slow heart rate during moderate exercise.
 3. Digoxin reduces the frequency of symptomatic paroxysmal attacks to a modest extent.
- During a 24 hour period, heart rate control is insufficient and may not protect the heart against potential risks of HF or cardiomyopathy associated with a persistent tachycardia. *Lancet* September 11, 1999; 882-83

9-14 CAN IT WORK? DOES IT WORK? IS IT WORTH IT?

1. Efficacy is the extent to which an intervention does more good than harm under ideal circumstances in a well designed, controlled trial. (Ie, can it work?)
 2. Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances in health care practice. (Does it work in practice?)
 3. Efficiency measures the effect of an intervention in relation to the resources it consumes. (Is it worth it?)
- BMJ* September 11, 1999; 319: 652-53

9-15 ARE SURROGATE MARKERS ADEQUATE TO ASSESS CARDIOVASCULAR DISEASE DRUGS?

Surrogate end points are thus neither consistent successes nor consistent failures. The safety concerns left unanswered by reliance on a surrogate need to be satisfied in some other way. *JAMA* August 25, 1999; 282: 790-91

9-16 PATERNALISM OR PARTNERSHIP?

Partners work together to achieve common goals. Their relationship is based on respect for each other's skills and competencies and recognition of the advantages of combining these resources to achieve beneficial outcomes.

Doctors are, or should be, experts in medical knowledge and applications. "The key to successful doctor-patients partnerships is recognizing that patients are experts too. Only the patient knows about his or her experience of illness, social circumstances, habits and behavior, attitudes to risk, values, and preferences." BMJ September 14, 1999; 319: 719-20

9-17 INSTILLING PROFESSIONALISM IN MEDICAL EDUCATION

The 3 essential characteristics of a profession:

1. Expert knowledge (as distinguished from a practical skill).
2. Self-regulation
3. Responsibility to place the needs of the client ahead of the self-interest of the practitioner. JAMA September 1, 1999; 282: 881-82

9-18 GAINING INFORMED CONSENT FOR SCREENING

"Because of the combination of benefit and harm in all procedures, the individuals being screened must receive full and accurate information about the procedure and must give their informed consent." "Failure to obtain informed consent for many current preventive interventions is clearly unethical." BMJ September 18, 1999; 319: 722-23

RECOMMENDED READING

- 9-9 FUNCTIONAL SOMATIC SYNDROMES: One or Many?
- 9-14 CAN IT WORK? DOES IT WORK? IS IT WORTH IT?
- 9-15 ARE SURROGATE MARKERS ADEQUATE TO ASSESS CARDIOVASCULAR DISEASE DRUGS?
- 9-17 INSTILLING PROFESSIONALISM IN MEDICAL EDUCATION
- 9-18 GAINING INFORMED CONSENT FOR SCREENING

REFERENCE ARTICLES

- 9-5 BRITISH HYPERTENSION SOCIETY GUIDELINES FOR HYPERTENSION MANAGEMENT 1999: Summary
- 9-10 GUIDELINES FOR HEALTHY WEIGHT
- 9-11 HOMOCYSTEINE IN HEALTH AND DISEASE

9-1 THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

Aldosterone has an important role in the pathophysiology of heart failure (HF). It promotes sodium retention, increases urinary loss of potassium and magnesium, activates the sympathetic system, inhibits the parasympathetic system, and impairs arterial compliance.

Angiotensin converting-enzyme (ACE) inhibitors suppress formation of aldosterone. The effect may be transient. Will spironolactone, an aldosterone-receptor blocker, complement the action of ACE inhibitors? Caution has been advised for fear that the combination will produce serious hyperkalemia.

This study tested the hypothesis that spironolactone, added to standard therapy, would reduce the risk of death among patients with severe HF due to systolic left ventricular dysfunction.

Conclusion: Spironolactone reduced risk of both morbidity and death.

STUDY

1. Double-blind multicountry study enrolled over 1600 patients (mean age 65). All had severe HF (most class III and IV) and left ventricular ejection fractions less than 35%.
2. All were being treated with ACE inhibitors, loop diuretics, and in most cases, digoxin. Potassium-sparing diuretics were not permitted.
3. Randomized to: 1) spironolactone 25 mg daily, or 2) placebo.

4. Follow-up = 2 years. (Trial discontinued early because efficacy was established.)

RESULTS

- | 1. Outcomes within 2 years: | Spirolactone | Placebo | NNT (benefit 2 years) |
|-----------------------------------|--------------|---------|-----------------------|
| Deaths | 35% | 46% | 9 |
| Hospitalizations for worsening HF | 26% | 40% | 7 |
2. Spirolactone was associated with lower risk of sudden death and death from progressive heart failure.
 3. Spirolactone group had a significant improvement in symptoms of HF.
 4. Adverse effects: Gynecomastia and breast pain in 10%. Eight percent discontinued spironolactone vs 5% in placebo group.
 5. Incidence of severe hyperkalemia was minimal in both groups. (Three patients in spironolactone group.)

DISCUSSION

1. Spirolactone was associated with lower incidence of death from all causes, fewer hospitalizations for cardiac causes, and improved symptoms of heart failure.
2. Benefits were observed within 2 months of treatment and persisted throughout the study.
3. It is likely that spironolactone has a direct cardioprotective effect.
4. Studies with combined spironolactone/beta-blocker are needed.
5. Standard doses of ACE inhibitors do not effectively suppress the production of aldosterone. Only the presence of an aldosterone blocker will completely suppress the effects of aldosterone.
6. The low incidence of hyperkalemia was likely due to use of relatively low doses of spironolactone (25 mg).
7. The benefits of combined ACE inhibitor and spironolactone in HF suggest combined use in other conditions — eg, hypertension and post myocardial infarction.

CONCLUSION

Blockade of aldosterone receptors by spironolactone, in addition to standard therapy with ACE inhibitors, loop diuretics, and digoxin substantially reduced risk of both morbidity and mortality among patients with severe HF.

NEJM September 2, 1999; 341: 709-17 Original investigation by the Randomized Aldactone Evaluation Study (RALES), first author Bertram Pitt, University of Michigan, Ann Arbor.

9-2 ALDOSTERONE AND SPIRONOLACTONE IN HEART FAILURE

(This editorial comments and expands on the preceding study.)

Congestive HF is a syndrome arising from hypoperfused tissues and congested organs. It has its pathophysiologic origins in salt-avid kidneys. The kidneys become adversaries of the heart, lungs, and liver. The house is divided; homeostasis is lost.

What accounts for this dysfunctional relationship? The answer is activation of the renin-angiotensin-aldosterone system.

Elevations of angiotensin II and aldosterone are physiologic when they preserve sodium and water homeostasis in response to sodium and volume contraction. In the absence of these circumstances, sustained activation of the renin-angiotensin-aldosterone system, as in HF, is inappropriate and pathologic. In HF, the potent actions of angiotensin and aldosterone overwhelm the ability of natriuretic peptides released by the distended heart to maintain euvoolemia and compensation. "Congestive heart failure is a result of circulatory balance gone awry."

In patients with HF, aldosterone (the sodium-retaining hormone) levels may be up to 20 times normal. This is due to increased production by the adrenal as a result of angiotensin stimulation and decreased plasma clearance by the liver related to reduced hepatic perfusion.

The importance of aldosterone in HF has been overlooked because ACE-inhibitors were thought to eliminate aldosterone production (by removing the angiotensin II stimulus to production). However, such suppression of aldosterone production is transient. The term "escape" has been used to describe this phenomenon. Aldosterone secretion proceeds independently of angiotensin concentrations.

Independent of the effect on sodium excretion, aldosterone has growth-promoting activity. Sustained elevations, together with sodium loading are accompanied by proliferation of fibroblasts and subsequent remodeling of atria, ventricles, and great vessels. Spironolactone prevents the fibrosis, independent of hemodynamic factors.

The study indicates that the beneficial effects of spironolactone in blocking aldosterone receptors are additive to those of ACE inhibitors. This is an important therapeutic advance. Therapy of HF should be broadened to include spironolactone as long as renal function is adequate.

NEJM September 2, 1999; 341: 753-54 Editorial by Anthony S Tavill, Case Western Reserve University School of Medicine, Cleveland, Ohio

Comment:

Spironolactone is an aldosterone antagonist — a competitive binder of aldosterone receptors. It is classified as a diuretic, causing sodium excretion and potassium retention. Thus, it acts directly in opposition to aldosterone which causes potassium excretion and sodium retention.

Spironolactone is available as a generic. RTJ

9-3 ZANAMIVIR FOR INFLUENZA: A Public Health Perspective

Serious complications of influenza, including death, are commonest in the elderly and in those suffering from "high risk" chronic illnesses. Immunization with inactivated flu vaccine is underused.

Now a new approach to preventing and treating influenza, inhibition of neuraminidase, is available. These drugs are active against both type A and B viruses. Zanamivir [Relenza] is available for use inhalation as a nasal spray or dry powder inhalation — ie, topical application. In experimental studies, zanamivir was reported to be safe and well tolerated. It is effective in preventing clinical influenza in healthy adults by about 66%. If infection occurs, the drug reduces duration of major symptoms by several days, and lowers complications of bronchitis and pneumonia, as well as use of antibiotics.

To be effective, it must be started within 30 hours of symptom onset.

This editorial comments that prescriptions may be demanded of general practitioners by patients who have symptoms compatible with influenza, who present early, and actually have a wide variety of other viral respiratory illnesses.

BMJ September 11, 1999; 319: 655-56 Editorial by Jonathan S Nguyen-Van-Tam University of Nottingham Medical School, UK.

Comment:

Glaxo-Wellcome has issued a warning letter to doctors concerning the possibility that the drug may cause bronchospasm and serious respiratory deterioration in some patients.

Special caution is needed when patients have underlying asthma or COPD. A fast-acting bronchodilator should be readily available.

The National Institute for Clinical Excellence (UK) has ruled that doctors in England and Wales should not prescribe zanamivir. On the basis that "No clear evidence exists for its safety and efficacy in patients with serious respiratory or cardiac disease as these patients have been excluded from clinical trials."

BMJ February 5, 2000; 320: 334 "News" by BMJ staff.

9-4 USE OF THE ORAL NEURAMINIDASE INHIBITOR OSELTAMIVIR IN EXPERIMENTAL HUMAN INFLUENZA

Neuraminidase is a major glycoprotein on the surface of both A and B influenza viruses. It is essential for sustained viral replication. Inhibition of the enzymatic action of neuraminidase causes the virus particles to aggregate at cell surfaces and with each other, and increases the ability of the respiratory mucosa to inactivate the virus.

Oseltamivir [Tamivir] is one of the new antiviral compounds designed and based on technology examining the crystallographic structure of neuraminidase. It can be given by mouth.

This study determined the safety, tolerability, and antiviral activity of oseltamivir for prevention and early treatment of experimental influenza.

Conclusion: The drug had significant preventive and treatment benefits.

STUDY

1. Randomized, double-blind, placebo-controlled study entered 117 healthy human volunteers. All had low titer of hemagglutination-inhibition antibodies. (I.e. were susceptible to influenza infection.)

(Although not stated, I presume none had received immunization. Ed.)

2. Inoculated intranasally all with live influenza virus.

3. Subjects were divided into 2 groups:

A. Prophylaxis study gave oral oseltamivir 100 mg once daily or 100 mg twice daily, or matching placebo starting 26 hours before virus challenge.

B. Treatment study gave the drug at the same doses, or matching placebo, starting 28 hours after virus challenge.

C. Treatment continued for 5 days.

RESULTS

| 1. Prophylaxis study: | Became infected ¹ | Infection-related illness ² | Shed virus |
|-----------------------|------------------------------|--|------------|
| Oseltamivir | 38% | 0 | 0 |
| Placebo | 67% | 33% | 50% |

(1 Positive culture or 4-fold or greater rise in antibody titers. 2 Infection-related respiratory illness.)

2. Treatment study:

All subjects became infected. Compared with the placebo group, viral titers were lower, duration of viral shedding shorter, concentrations of nasal proinflammatory cytokines lower, and symptom scores reduced.

3. Adverse effects: Transient mild to moderate nausea in 17% of oseltamivir subjects vs 7% of placebo subjects. This occurred mainly with the 200 mg dose, and was largely prevented when the drug was given with food. (Indeed, administration with food modestly increases bioavailability.)

DISCUSSION

1. Oral administration of oseltamivir provided significant antiviral, biochemical, and clinical effects in experimental influenza infection.

2. The effects were similar to those reported in earlier studies with intranasal zanamivir. This would predict that oseltamivir should be associated with both prophylactic and therapeutic activity against natural influenza.

3. With respect to prophylaxis, an antiviral dose that allows for a subclinical but immunizing infection would be optimal.

4. Initial results indicate that once daily dose of 75 mg is safe and effective for prophylaxis, and 75 mg twice daily safe and effective for short-term treatment.

CONCLUSION

Prophylaxis and early treatment with oral oseltamivir were both associated with significant antiviral and clinical effects in experimental human influenza.

JAMA October 6, 1999; 282: 1240-46 Original investigation, first author Frederick G Hayden, University of Virginia Health Sciences Center, Charlottesville.

See also: "Use of the Selective Oral Neuraminidase Inhibitor Oseltamivir to Prevent Influenza" NEJM October 28, 1999; 341: 1336-43

This study compared oseltamivir with placebo given for 6 weeks for prophylaxis during a winter flu season. None of the subjects had received influenza vaccine. The drug was effective in preventing naturally occurring influenza —about 75% effective protection against laboratory confirmed illness. The six week course was safe, with nausea and vomiting being the main adverse effects. Risk of infection was 1.2% in the treated group and 4.8% in the placebo group. Thus 3.5% were protected. NNT(benefit)= 28.

Comment:

What is the clinical message for primary care? I believe use should be restricted. Vaccination is still the basic prophylaxis. Availability of a drug for treatment and prophylaxis should not deter immunization. I have seen no studies for effectiveness of oseltamivir in immunized persons. Certainly the NNT for prevention of infection will be much higher than 28 in immunized persons.

Neuraminidase inhibitors are an entirely new class of drugs. Nothing like them before. Consequently long-term postmarketing use will be needed to determine overall toxicity. Safety of use in immunocompromised patients and patients with liver and kidney disease is undetermined.

Patients may likely ask clinicians for prescriptions for flu-like illnesses that are not influenza. Use should be restricted to a well established flu season for patients with typical symptoms. The wily flu virus may mutate to escape effect of the drug, raising another problem of wide-spread usage. RTJ

REFERENCE ARTICLE

9-5 BRITISH HYPERTENSION SOCIETY GUIDELINES FOR HYPERTENSION MANAGEMENT 1999: Summary

This article summarizes guidelines for management of hypertension. Since previous British guidelines (1989 and 1993), new evidence has emerged on optimal BP targets; management of hypertension in diabetic persons; treatment of isolated systolic hypertension; comparison of the antihypertensive efficacy and tolerability of different drug classes; the role of non-pharmacological measures for prevention and treatment of hypertension; and additional benefits associated with the use of aspirin and statins.

Summary points:

- * Use non-pharmacological measures in all hypertensive and borderline hypertensive people.
- * Initiate drug therapy in people with sustained systolic BP ≥ 160 or sustained diastolic BP ≥ 100 .
- * Decide on treatment in people with sustained systolic BP between 140 and 159 or sustained diastolic BP between 90 and 99 according to the presence or absence of target organ damage, cardiovascular disease, diabetes, or a 10-year risk of coronary heart disease $\geq 15\%$.
- * Optimum targets are systolic < 140 and diastolic < 85 . The minimal acceptable level of control recommended is < 150 and < 90 .

Lowering to $< 140/80$ is recommended in persons with diabetes.

- * In the absence of contraindications or compelling indications for other antihypertensive agents, thiazide diuretics and beta-blockers are preferred as first line treatment for the majority of hypertensive people.
- * Other drugs that reduce cardiovascular risk must be considered, including aspirin and statins.

For a concise algorithm of management, starting with initial BP readings, see figure p 632

Compelling reasons for use of drugs other than diuretics and beta-blockers include prostatism, heart failure, myocardial infarction, isolated systolic BP in the elderly, and angina, (See table 1 p. 632)

"Most hypertensive people will require combinations of antihypertensive therapy to achieve optimal control. Drugs from different classes have additive effects on blood pressure when they are prescribed together. Submaximal doses of two drugs result in larger responses of blood pressure and fewer side effects than maximal doses of a single drug."

"Statin treatment could now be justified at a 10 year coronary heart disease risk of 6%, but this would entail treating over half of all hypertensive patients. The main constraint at present is cost."

BMJ September 4, 1999; 319: 630-35 Review article, first author Lawrence E Ramsay, University of Sheffield, UK

1 Several methods which estimate risk of cardiovascular events have been published. One, by the National Heart Foundation of New Zealand appears in the issue (December 1999) of "Clinical Evidence" Calculation of the absolute over 5 years is based on: sex; age; diabetes (yes or no); smoking (yes or no); BP at various ranges; and ratio of total to HDL-cholesterol. Benefits of reducing total cholesterol by 20% and reducing BP by 10 to 15/5 to 8 mm Hg are expressed as NNT for 5 years to prevent one event.

Two editorials comment on this guideline 1,2

The new guidelines take the radical step of advocating the use of cardiovascular risk assessment to rationalize clinical decision making in patients with mild or borderline hypertension. Ie, for patients with target organ damage, history of cardiovascular disease, diabetes, lipid disorders, or otherwise at higher risk for coronary heart disease, BP control is started at a lower level and the recommended target levels are reduced.

Aspirin is recommended in patients with hypertension over age 50, have target organ damage, diabetes, or a 10-year risk of coronary heart disease greater than 15%. Use should begin only after BP is controlled to less than 150/90

Statin drugs are recommended for primary prevention of cardiovascular disease if the total cholesterol is over 190 mg/dL and when 10-year risk for CHD is greater than 30%

(Ie, hypertension is not treated in isolation. All risk factors for cardiovascular disease are treated together. Ed.)

"The absolute benefit from treatment in the elderly is much larger than that for younger hypertensives because of their higher absolute risk." "There was a widely and incorrectly held view that a rise in blood pressure with age was inevitable and harmless. There were also fears that the elderly would not tolerate antihypertensive drugs." The new guidelines recommend BP screening should be continued until at least age 80. If drug treatment was started before then, it should be continued.

All drugs approved for treating hypertension lower BP. But the purpose of treatment is to reduce the risk of complications such as myocardial infarction, stroke, and heart failure. Only low dose diuretics and beta-blockers have consistently passed this standard of evidence. Recommendations for various "compelling" and "possible" indications are consensus based, rather than evidence based. Indeed, the differences between British and American recommendations for "possible" indications . . . "is striking and sometimes looks like the result of special pleading".

The level of BP at which drug treatment is begun (and which drugs to use) still may depend on patient preference.

1 BMJ September 4, 1999; 319: 589-90

2 Lancet September 4, 1999; 354: 839

9-6 ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND MORTALITY, MYOCARDIAL INFARCTION, AND STROKE IN 25 YEAR FOLLOW UP OF 49 618 YOUNG SWEDISH MEN

Several epidemiological studies have shown that moderate alcohol consumption is associated with reduced mortality from cardiovascular diseases in middle aged and elderly subjects. This study asked — does this association hold in younger men.?

Conclusion: Alcohol was associated with increased risk in younger men.

STUDY

1. In 1969-70 entered over 49 000 military conscripts born between 1949 and 1952. (Age at entry = 17 to 21.)

2. Questionnaires determined alcohol use at baseline — quantity and frequency of different alcoholic beverages. Calculated usual consumption in terms of grams of 100% ethanol per day.
3. Determined relative risks of myocardial infarction (MI), stroke, and death associated with alcohol consumption.
4. Follow-up = 25 years — from about age 20 to 45.

RESULTS

1. Over 25 years (over age span from about 20 to 45) total mortality = 1473; myocardial infarctions = 279 (38 fatal); stroke = 233 (30 fatal).

| 2. Adjusted relative risks (RR): | Death | Myocardial infarction | Stroke |
|----------------------------------|-------|-----------------------|--------|
| Abstainers | 1.00 | 1.00 | 1.00 |
| 1-14 g ethanol / day | 1.13 | 0.90 | 1.59 |
| 15-30 | 1.32 | 0.77 | 1.52 |
| > 30 | 1.53 | 0.61 | 2.30 |

3. Adjusted RR of death and stroke increased with increasing consumption of alcohol. RR for MI decreased with increasing intake.

4. "To a considerable extent, the increased mortality with high alcohol consumption was due to the strong association between drinking and smoking."

5. The calculated attributable proportion of outcomes from drinking, relative to abstention, was 14% for death (alcohol use caused 205 deaths); 37% for stroke (causing 86 strokes). Alcohol prevented 44 myocardial infarctions (16%).

6. There was a clear association between the level of alcohol use and risk of subsequent hospitalization with a diagnosis of alcoholism, alcohol psychosis, and alcohol intoxication.

7. The results also indicate a cardioprotective effect in these relatively young men in whom MI is rare.

CONCLUSION

Alcohol clearly had a negative net effect on health up to age 45. This supports a restrictive alcohol policy with recommendations for little or no alcohol consumption by young men.

BMJ September 25, 1999; 319: 821-22 Original investigation by Anders Romelsjo and Anders Leifman, Karolinska Institute, Sweden.

Comment:

This is not exactly news, but bears repeating. The young are most susceptible to the adverse effects of alcohol.

I read somewhere a quote from a sage — Anyone younger than 50 who drinks is just as foolish as anyone over 50 who does not drink. RTJ

9-7 FUNCTIONAL FOODS

"Functional food' has become a buzz word both in nutrition research and the food industry. The term hints of a future in which specially developed foods will protect consumers from a variety of diseases and discomforts. How realistic is this expectation?"

What are functional foods (FF)? A recent consensus statement states that a food can be regarded as "functional" if it has beneficial effects on "target" functions in the body, beyond adequate nutritional effects, in a way that is relevant to health and well-being and/or a reduction of disease.

The Unilever food company defines FF as a "Food with a health claim based on scientific evidence".

In the U.S., the Dietary Supplement and Health Education Act of 1994 relaxed the restrictions on health claims for food supplements and allowed manufacturers to describe beneficial effects of supplements or dietary ingredients on "structure or function" of the body or on "well-being", without permission of the FDA. Thus manufacturers became free to advertise benefits without rigorous proof. The market has been in the billions.

The claim on the label is an essential part of any functional food or supplement (the border between the two is hard to define). For example: bran relieves constipation; unsaturated fatty acids reduce cholesterol and risk of coronary heart disease; foods high in potassium

and low in sodium reduce blood pressure. These effects have been known for a long time. Producers of FF are looking for new active ingredients, preferably those that can be patented.

Several candidates are in the running as ingredients for FF:

- * Margarine with added plant sterols reduce cholesterol. There is debate whether these sterols are a food or a drug.
- * Antioxidants. Vitamin E studies have reported conflicting results of benefits.
- * Vitamins. Clinical trials of large intakes of B vitamins, especially folic acid, vitamins B6, and B12 are ongoing to determine if their effect on reducing homocysteine levels will protect against cardiovascular disease.
- * N-3 fatty acids found in fish and certain vegetable oils. Preliminary studies report a benefit in preventing ventricular fibrillation and sudden death.
- * In addition, there are interesting developments relating dietary ingredients to growth, development and differentiation, immune response, gastrointestinal function, and behavior.

Nutritional research is expensive and slow. Results often fail to substantiate high hopes. Some companies may therefore be tempted to forego rigorous testing and put foods on the market with unsupported health claims. Better regulation of functional and health claims for foods and supplements is needed to assure that such claims are based on solid evidence.

Lancet September 4, 1999; 354: 794 Editorial by Martijn B Katan, Wageningen Agricultural University, Netherlands.

9-8 ULTRASONOGRAPHY AND LIMITED COMPUTED TOMOGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF APPENDICITIS IN CHILDREN

The use of ultrasonography (US) in the diagnosis of childhood appendicitis has increased steadily. However, it is highly operator dependent and rarely visualizes either an inflamed retrocecal appendix or a non-inflamed appendix.

Advances in computed tomography (CT) have yielded sensitivities as high as 100% and specificities as high as 98% for the diagnosis of appendicitis in adults.

This study determined prospectively the accuracy of US followed by limited CT. (I.e, CT with contrast material administered only through the rectum).

Conclusion: CT following a negative or indeterminate US was highly accurate in diagnosis.

STUDY

1. Prospectively followed a subset of 108 children and adolescents who presented to ER with suspected appendicitis. This was a subset in which the diagnosis was difficult. Those with clear clinical signs and symptoms of appendicitis (with or without US confirmation) were excluded from the study. They went on to immediate surgery.
2. All 108 received a US study which was equivocal or indeterminate. CT was then performed.
3. Patients who did not undergo surgery were followed up clinically for 2 weeks.

RESULTS

1. A total of 108 patients received CT. (See figure 2 p 1044)
 - A. CT indicated appendicitis in 30 patients. (Positive test)
 - Of these, 28 patients actually had appendicitis. (True positive = 28; false positive = 2; false positive rate = 6%)
 - B. CT did not indicate appendicitis in 75; was equivocal in 3. (Negative test)
 - 74 of the 78 did not have appendicitis on clinical follow-up, 4 did. (True negative = 74; false negative = 4; false negative rate = 5%)
2. CT correctly changed management in 73% of this series of children.

DISCUSSION

1. In the adult population, CT with rectal contrast has been shown to be 98% accurate in the diagnosis of appendicitis. It is safe, can be performed quickly, and improves patient care while decreasing costs.
2. In this series, CT was evaluated in a group of children in whom the diagnosis was difficult — those with equivocal clinical findings and negative or indeterminate US.
3. When a patient is suspected on clinical grounds of having appendicitis, a negative US is not likely to dissuade a surgeon from operating. Management strategies are rarely based on negative sonographic findings.
4. CT, on the other hand, increases the sensitivity of diagnosis. It increases the surgeon's confidence. If negative, the patient is very unlikely to have appendicitis; if positive the patient is very likely to have appendicitis.
5. "We believe that CT should be reserved for those children in whom, after full clinical evaluation, the diagnosis remains uncertain." In these patients, who have a low probability of appendicitis, a positive US will be able to diagnose appendicitis in about 40%. (I.e, US is a useful primary diagnostic test.) But, a negative US will not rule out appendicitis. CT is then recommended.
6. There may be a subset of children for whom CT may be justified without a preliminary US.

CONCLUSION

CT following a negative or indeterminate ultrasound was highly accurate in the diagnosis of appendicitis. JAMA September 15, 1999; 282: 1041-46 Original investigation, first author Barbara M Garcia Pena, Children's Hospital, Harvard Medical School, Boston, Mass.

Comment:

Some articles present confusing data. In this article, I had difficulty in correlating the data in the written text with the figure and the tables. Table 2 p 1045 is especially confusing. This makes the article difficult to interpret. Surely, editors and authors can collaborate to present data more clearly.

My calculations of false positive and false negative rates differ slightly from those presented by the authors. This does not change the conclusions. RTJ

Read the Original !

9-9 FUNCTIONAL SOMATIC SYNDROMES: One or Many?

This article reviews the concept and importance of somatic symptoms and syndromes. On the basis of a literature review, the authors conclude that a substantial overlap exists between the individual syndromes, and that similarities between them outweigh the differences. Many patients with different functional syndromes also share non-symptom characteristics. Similarities are apparent in case definition, reported symptoms, and in non-symptom associations such as patients' sex, outlook, and response to treatment.

Functional somatic syndromes by specialty:

| | |
|---------------------------|---|
| Gastroenterology | Irritable bowel syndrome; non-ulcer dyspepsia |
| Gynecology | Premenstrual syndrome; chronic pelvic pain |
| Rheumatology/Fibromyalgia | |
| Cardiology | Atypical of non-cardiac pain |
| Respiratory medicine | Hyperventilation syndrome |
| Infectious diseases | Chronic (postviral) fatigue syndrome |
| Neurology | Tension headaches |
| Dentistry | Temporomandibular joint dysfunction; atypical facial pain |
| Ear, nose and throat | Globus syndrome |
| Allergy | Multiple chemical sensitivity |

The authors conclude that the existing definitions of these syndromes in terms of specific symptoms is of limited value. Instead they believe an inclusive classification is likely to be more productive.

The authors postulate that the existence of specific somatic syndromes is largely an artifact of medical specialization. That is — the differentiation of specific functional syndromes reflects the tendency of specialists to focus on only those symptoms pertinent to the specialty.

There is a similarity in the treatments recommended for patients with various functional somatic syndromes. There is similarity in response to treatment. "At present, the hypothesis that all functional syndromes respond to the same therapies seems to be partly supported."

The authors propose "An end to the belief that each "different" syndrome requires its own particular subspecialist to adopt an idiosyncratic approach in apparent isolation... ."

Lancet September 11,1999; 354: 963-39 Editorial review, first author S Wessely, Guy's, King's, and St Thomas' School of Medicine, London, UK

Comment:

An interesting concept. The authors are lumpers rather than splitters. I suspect many patients with the various syndromes do indeed have much in common. And that the approach to management is similar; treatment difficult. RTJ

=====REFER
ENCE ARTICLE

9-10 GUIDELINES FOR HEALTHY WEIGHT

I abstracted a few points. Ed.:

A primary use of weight guidelines is to provide direction for healthy persons. Periodic measurements are recommended for all patients.

Adult weight:

Among middle-aged adults body mass index (BMI —weight in kg divided by height in cm²) is strongly correlated with fat mass measured densitometrically.

Weight guidelines inevitably represent a somewhat arbitrary compromise. The lower boundary for a healthy weight has been set at a BMI of approximately 19; the upper boundary approximately 25.¹ This is based on mortality outcomes. Mortality is increased considerably above 25.

A table on p 428 gives US guidelines for height in inches and weight in pounds corresponding to a BMI range of 19 to 25.

But, risks of diabetes, hypertension, and coronary disease increase at levels well below 25. Risk of coronary heart disease in women with a BMI of 26 is about twice the risk of women with a BMI less than 21; for men risk is about 1.5. For the same comparison, risk of diabetes is 4 to 8 times higher; risk of hypertension 2 to 3 times higher. With a BMI of 29 or higher, risks are higher still.

Even small gains in weight within the range of healthy weights can carry health risks. Physicians should counsel their adult patients to make small but permanent adjustments in physical activity and eating patterns if they approach the upper limit of the range for healthy weight.

"The road to prevention must begin with an increased awareness of even small weight gains and the counseling of patients to modify their diet and activity patterns appropriately."

Weight gain after age 21:

Weight gain more than 10 pounds after age 21 should be avoided. A major limitation of standard weight guidelines is that a person initially at the low end of BMI can gain as much as 15 to 20 pounds and still remain within the recommended range. But such gains, and even smaller gains, are associated with significantly increased risks. Even a small gain (eg, 10 pounds) which occurs after adult height is

attained calls for advice to modify food intake and exercise. Individuals who, as they grow older, maintain their weight close to that of age 18, are at less risk of diabetes, coronary disease and hypertension than those who gain 10 to 20 pounds.

Abdominal circumference:

A large or increasing abdominal circumference is due to excess fat (after ascites is ruled out). Excess intraabdominal (visceral) fat is a potential risk factor for chronic diseases.

Attention to increases in waist circumference by 2 inches or more is also appropriate, even if weight has remained stable or within the range of healthy weights.

A circumference over 40 inches (102 cm) for men and 35 inches (89 cm) for women are suggested cut points.

Patients already overweight:

For patients who are already overweight, weight guidelines should not be used to define goals for weight reduction, because, for seriously overweight persons, the range of healthy weights is often unachievable. Reductions of even 5% or 10% can substantially improve blood pressure, lipid levels, and incidence of hypertension and diabetes.

NEJM August 5, 1999; 427-34 Review article, first author Walter C Willett, Brigham and Woman's Hospital and Harvard Medical School, Boston Mass.

1 Department of Agriculture Dietary Guidelines 1995

REFERENCE ARTICLES

9-11 HOMOCYSTEINE IN HEALTH AND DISEASE

The theory that moderately elevated plasma levels of homocysteine may be a cardiovascular risk was published in 1975. Homocysteine levels may be determined by both genetic and nutritional factors. Genetic causes are mostly defects in enzymes that control homocysteine metabolism. Nutritional causes are deficiencies of folate, vitamin B6, and vitamin B12, all of which affect homocysteine metabolism.

A study published in this issue of *Annals*¹ reported a mortality hazard ratio of 2.0 when comparing subjects in the highest fifth of homocysteine plasma level distribution with those in the lowest fifth. Ten percent of deaths were attributable to homocysteine levels over 14 mmol/L. These findings are supported by a recent Framingham study, which also reported an increased risk of both all cause, and cardiovascular mortality related to high plasma homocysteine.

The epidemiological evidence connecting risk with elevated levels is consistent, strong, and biologically plausible. The risk is also independent of other risk factors.² But data from prospective studies are weaker, with some conflicting results. Causality has not been proven.

Plasma homocysteine is a sensitive marker for folate and vitamin B status. Levels of homocysteine are inversely related to plasma levels of these vitamins. An increase in homocysteine concentrations occurs long before classic deficiency is evident.

High levels of homocysteine may add to the conventional risk factors for cardiovascular disease. Thus, it may be particularly important for individuals with high levels to avoid smoking, and control lipids and hypertension.

A study also reported in this issue of *Annals*³ defines reference ranges for total plasma homocysteine among persons who are folate and vitamin B12 replete and have normal creatinine concentrations. Levels increase with age. In most cases high concentrations were associated with low vitamin concentrations.

Hyperhomocysteinemia occurs most often in persons with inadequate folate status — much more frequently than with low vitamin B12 status.

What is the clinical message? "It may be reasonable now to suggest folic acid supplementation in dosages of 0.4 to 1.0 mg/d for high-risk persons with elevated homocysteine levels and to encourage eating of plenty of fruit and vegetables for the rest of us."

1 "Nonfasting Plasma Total Homocysteine Level and Mortality in Middle-aged and Elderly Men and Women in Jerusalem" Annals Int Med September 7,1999; 131: 321-30

2 "Homocyst(e)ine and Cardiovascular Disease: A Critical Review of the Epidemiologic Evidence." Annals Int Med September 7,1999; 131: 363-75

3 "Serum Total Homocysteine Concentrations in the Third National Health and Nutrition Examination Survey (1991-94): Population Reference Ranges And Contribution Of Vitamin Status to High Serum Concentrations" Annals Int Med September 7, 1999; 131: 331-39

Comment:

I suspect thousands of physicians are now taking daily multivitamin supplements containing folic acid for primary prevention, joining those who take a daily low-dose aspirin. RTJ

9-12 HOME MADE SPACERS FOR BRONCHODILATOR THERAPY IN CHILDREN WITH ACUTE ASTHMA

A pressurized metered-dose inhaled (MDI) with attached spacer can produce the same or better bronchodilation than a nebulizer even in the presence of severe airways obstruction. Ease of use and low cost are additional advantages. A spacer is essential to minimize dependence on the patient's inhalation technique and to optimize drug delivery.

Expense and lack of availability limit use of spacers in developing countries.

Previous studies have demonstrated that aerosol deposition of the nebulized drug on the spacer is the same whether a conventional spacer is used, or a sealed 500 mL plastic cold-drink bottle is used.

This study tested the efficacy of a home-made spacer (500 mL plastic bottle) vs a conventional spacer for delivery of a beta-2 agonist via MDI in children with acute asthma.

Conclusion: The home-made spacer gave clinically significant bronchodilation and improvement in symptoms.

STUDY

1. Entered 88 children with acute asthma.
2. Gave the beta2 agonist fenoterol via MDI into: 1) a conventional spacer, 2) sealed 500 mL bottle, 3) unsealed 500 mL bottle, and 4) 200 mL polystyrene cup. (See figure 1 p 980 for illustration of the use of the MDI with bottle spacer. The base of the plastic bottle around the inserted MDI was sealed with glue. The opposite end was held in the mouth to simulate a mouthpiece.)
3. Measured increases in forced expiratory volume in 1 second (FEV1) and peak expiratory flow after treatments.

RESULTS

1. For 44 children with moderate to severe asthma:

| A. | Increase in FEV1 | Increase in PEF |
|--------------------|------------------|-----------------|
| Plastic cup | 0% | 12% |
| Unsealed bottle | 18% | 21% |
| Sealed bottle | 33% | 36% |
| Conventional space | 37% | 59% |

B. Follow-up nebulization was required in 10 of 11 who used the cup; 9 of 11 who used the unsealed bottle; 8 of 11 who used the sealed bottle; 4 of 11 who used the conventional spacer.

2. For 44 children with mild asthma, response to bronchodilator was similar for all 4 spacers.

DISCUSSION

1. "A 500 ml plastic bottle and a conventional spacer gave a similar response to a beta2 agonist given by MDI."
2. Differences in response were most apparent in children with moderate to severe asthma.
3. The dimensions of the 500 mL bottle are similar to the conventional spacer. (About 11 cm long and 3.5 cm in diameter.)
4. For optimum benefit, the MDI must be sealed in the bottom of the plastic bottle. A heated wire the same size and shape as the MDI was applied to the base of the bottle to melt the bottle and make a hole for fitting and creating a tight fit.
5. The plastic bottles were primed with 15 puffs of bronchodilator to reduce the electrostatic charge of the sidewalls and to optimize delivery.
6. The bottle is limited in that it has no one-way valve. Thus, exhaled air may enter the spacer. In the experience of the investigators, absence of the valve did not adversely affect response.

CONCLUSION

A 500 mL plastic bottle is an effective alternative to a conventional spacer. It may be a valuable application in developing countries.

Lancet September 18, 1999; 354: 979-82 Original investigation, first author H J Zar, University of Cape Town, South Africa.

9-13 DIGOXIN IN THE TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION

Although atrial fibrillation (AF) may be symptomless in some patients, it causes substantial morbidity. Clinical features include palpitations, dyspnea, (pre)syncope, angina, heart failure (HF), and increased risk of thromboembolism. AF is associated with increased mortality.

Patients with persistently rapid heart rates are at risk of developing tachycardia-induced cardiomyopathy.

Most patients require treatment to alleviate symptoms. Two therapeutic strategies may be pursued: 1) restore and maintain sinus rhythm, and 2) accept the arrhythmia and control the ventricular rate. With either strategy, measures to prevent thromboembolic complications should be instituted except in low risk patients.

Restoration of sinus rhythm is preferred for patients with acute, recent-onset (< 48h) paroxysmal AF. Rate control is the goal in patients with permanent AF or in those with frequent long (>48h) attacks who have not responded to conversion therapy.

Digitalis has long been a front runner for treatment of AF. It has been recommended for: 1) conversion of paroxysmal AF to sinus rhythm, 2) prevention of recurrences, and 3) slowing the ventricular rate when AF persists. Digoxin has been reported to reduce the heart rate at the onset of a paroxysm, rendering the subsequent attack more tolerable.

How valid are these claims? They have been challenged recently by well-designed clinical studies which report:

1. In the absence of HF, digoxin has no effect on the conversion rate of AF of recent (< 7 days) onset.
2. Digoxin has a significant, albeit clinically modest, effect on reducing mean ventricular rate in symptomatic attacks. (Eg, reduction to 125 beats/min compared with 138 for placebo.) However, digoxin does not slow heart rate during moderate exercise.
3. Digoxin reduces the frequency of symptomatic paroxysmal attacks to a modest extent.
4. During a 24 hour period, heart rate control is insufficient and may not protect the heart against potential risks of HF or cardiomyopathy associated with a persistent tachycardia.

Digoxin may be used as first-line treatment for both rate control and prophylaxis when AF is associated with signs of HF. In these circumstances, the inotropic effect of digoxin may indirectly produce a beneficial effect.

Lancet September 11, 1999; 882-83 Editorial, first author Etienne O Robles, University Medical Center, Utrecht Netherlands.

Comment:

Old timers relied heavily on digoxin treatment of AF. Anecdotally, starting therapy was often associated with conversion to sinus rhythm. And ventricular rate was controlled adequately in many patients. RTJ

Read the Original!

9-14 CAN IT WORK? DOES IT WORK? IS IT WORTH IT?

The British pioneer clinical epidemiologist, Archie Cochran, defined 3 concepts related to testing healthcare interventions:

1. Efficacy is the extent to which an intervention does more good than harm under ideal circumstances in a well designed, controlled trial. (Ie, can it work?)
2. Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances in health care practice. (Does it work in practice?)
3. Efficiency measures the effect of an intervention in relation to the resources it consumes. (Is it worth it?)

Almost all clinical trials measure efficacy. Trials typically select patients who are carefully diagnosed; are at highest risk of adverse outcomes from the disease in question; lack other serious illnesses; and are most likely to follow and respond to the treatment of interest. (Ie, can it work under optimum circumstances?) If the intervention does not work under such ideal conditions, it surely will not work under usual conditions. (Ie, it will not work in the real world.)

Effectiveness in the community depends not only on efficacy, but also on diagnostic accuracy, provider compliance, patient adherence, and the health services available. (Also on comorbidity — lack of other serious illnesses. Ed.)

There are multiple barriers to doing health services research and implementing innovative health services. This is why so few investigators try to do effectiveness studies. And even if they succeed, healthcare managers, planners, and politicians will want to know much more than does it work in usual practice? They want to know "Is it worth it?" in comparison to use of the resources for other needs.

"We need more effectiveness studies to sort the fool's gold from the true gold, and efficiency studies to tell us if the price of extraction is a bargain."

BMJ September 11, 1999; 319: 652-53 Essay by Brian Haynes, McMaster University Health Sciences Center, Hamilton, Ontario, Canada.

Comment:

Considering the benefit/harm-cost ratio of an intervention is a supplemental way of viewing these concepts. RTJ

Read the Originals!

9-15 ARE SURROGATE MARKERS ADEQUATE TO ASSESS CARDIOVASCULAR DISEASE DRUGS?

A surrogate end-point or marker has been defined as — "A laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point." The surrogate is expected to predict the effect of the therapy. A clinically meaningful end point is a direct measure of how a patients feels, functions, or survives. An effect of the surrogate is not per se of any value to the patients. It is a benefit only to the extent that it causes or predicts an improved outcome (fewer myocardial infarctions, strokes, or deaths). There is a mixed response to use of surrogate end points as a basis for reaching conclusions about benefits of therapy. Using a surrogate to predict clinical results before clinical outcomes are established could bring useful applications years earlier, and at lower costs than waiting for clinical proof. Conversely, reliance on a surrogate, which ultimately does not lead to clinical benefit, can lead to adoption of useless or even harmful therapies.

Surrogate end points are important early in the evaluation of drugs in development. But, their use in the drug-approval process for treatment of what are generally asymptomatic risk factors does not provide an evaluation of meaningful clinical effectiveness. Their use limits ability to assess safety by permitting evaluation of the drug in fewer people exposed for a shorter time.

"In the late 1990s, millions of Americans are taking antihypertensive and antidiabetic therapies that have not been adequately evaluated in large, long-term clinical trials. Despite the widespread use of calcium channel blockers, angiotensin-converting enzyme inhibitors, alpha-blockers, sulfonylureas, metformin, and troglitazone, their optimal role in the treatment of hypertension and type 2 diabetes based on clinical trials remains unclear."

The editorialist suggests that new drug therapies be regularly evaluated in long-term phase 4 trials (postmarketing use in the general public) after approval. This approach is a compromise. Requirements for long-term clinical trials before approval would slow the time for approval and meet resistance from those who advocate shortening the time to approval.

JAMA August 25, 1999;282: 790-91 Editorial by Robert Temple, Center for Drug Evaluation and Research Policy, FDA, Rockville Md.

An editorial in this issue "Surrogate Endpoints, Health Outcomes, and the Drug-approval Process for the Treatment of Risk Factors for Cardiovascular Disease" JAMA August 25, 1999; 282: 786-95 comments:

In many cardiovascular diseases, surrogate endpoints have not proved reliable predictors of outcome, the most striking examples being the failure of effects of antiarrhythmic drugs on VPB (ventricular premature beats) rates to improve survival and the similar failure of inotropic and vasodilator drugs to improve heart failure outcome. On the other hand, many studies have shown that the ability of drugs to lower blood pressure predicts outcome, and the large effects on cholesterol induced by HMG-CoA reductase inhibitors (statin drugs) are also establishing a pattern of improved outcome. Surrogate end points are thus neither consistent successes nor consistent failures. The safety concerns left unanswered by reliance on a surrogate need to be satisfied in some other way.

Comment:

Use of a surrogate is based on its biological plausibility. The main concern is long-term safety. This reinforces the older clinicians' admonition not to be the first to use a newly introduced drug if other drugs of long-standing are available for the same purpose. Wait for a few years of postmarketing until the safety of the new drug is more clearly demonstrated.

Even if the older drugs have never been subject to a definitive randomized, controlled trial, their safety is better known. RTJ

9-16 PATERNALISM OR PARTNERSHIP?

Patients have grown up — and there's no going back

Paternalism has the effect of creating and maintaining an unhealthy dependency which is out of step with other currents in society.

This issue of BMJ presents articles assembled to consider the scope of creating meaningful partnerships between doctors and patients, and between health policymakers and local communities.

Partners work together to achieve common goals. Their relationship is based on respect for each other's skills and competencies and recognition of the advantages of combining these resources to achieve beneficial outcomes.

Doctors are, or should be, experts in medical knowledge and applications. "The key to successful doctor-patients partnerships is recognizing that patients are experts too. Only the patient knows about his or her experience of illness, social circumstances, habits and behavior, attitudes to risk, values, and preferences."

"The problem with consumerism is that it encouraged people to make demands, but failed to emphasize reciprocal responsibilities. The new emphasis is on shared information, shared evaluation, shared decision making, and shared responsibilities."

Younger people tend to be more critical of professional paternalism and more likely to expect active participation in decisions about their care. Some older patients and some with serious illnesses prefer to defer decision making to the doctor, perhaps because it allows them to avoid responsibility. For doctors the trick will be to determine which patients want to be offered choice, and which prefer a more passive role. The requirements of informed consent require some level of patient engagement with decision making. "But, in an eight minute consultation how feasible is it to determine patients' preferences and sensitivities and provide full and unbiased information?"

BMJ September 14, 1999; 319: 719-20 Editorial by Angela Coulter, King's Fund, London, UK

Comment:

Partnership in clinical decision making requires an informed, intelligent, interested, and engaged patient. Many (indeed, I believe most) patients consulting primary care providers do not meet these requirements — the illiterate, those of different cultures and languages, the very old, the demented. They do not, or cannot, grasp the concept of autonomy; have not thought about it; have not related it to the medical encounter.

How is the clinician to develop a partnership with these patients? Perhaps a few can be reached through family or friends. Are clinicians to pause in the middle of a consultation to explain the ethical dimensions of autonomy? I suspect most clinicians will, relying on their own ethical interpretations, remain paternalistic, and act in the patient's "best interest". I believe partnership-autonomy is a worthwhile eventual goal, but it will be a long-time coming. RTJ

Read the Original!

9-17 INSTILLING PROFESSIONALISM IN MEDICAL EDUCATION

The 3 essential characteristics of a profession:

1. Expert knowledge (as distinguished from a practical skill).
2. Self-regulation
3. Responsibility to place the needs of the client ahead of the self-interest of the practitioner.

There is renewed interest in the third, or altruistic, character of the medical profession. Ie, maintaining patient interest above physician self-interest.

Now, market forces pose an unprecedented threat to medical professionalism — particularly the physician's obligation to serve the needs of patients. "For all its defects, the fee-for-service system that long dominated medicine had one great advantage: it allowed physicians to do what was necessary for patients. In contrast, today's managed care environment has undermined physicians' ability to provide needed care. Many managed care organizations, whether seeking to control costs or maximize profits, have created strong financial incentives for physicians to restrict care. This raises the specter of "double agents" who would purportedly serve the patient, but in fact limit care for the financial benefit of the employing organization."

"For more than 30 years, public charges that physicians are impersonal, self-serving, greedy, and occasionally dishonest have been increasing — despite the expanded teaching of medical humanities and ethics at medical schools."

Instruction and mentoring (role-modeling), even when offered together in medical schools, account for only some of the factors that influence development of professionalism. The entire institutional environment of the academic health center plays a role on shaping the attitudes, values, beliefs, modes of thought, and behavior of medical students. Attitudes are shaped by the totality of students' interaction with faculty, house officers, patients, hospital staff, and one another. "An unfriendly institutional culture can easily undermine the well-intentioned efforts of those trying to impart professionalism." The effect of a brilliant lecture to assembled students can easily be undone should the student return to the ward and hear the resident speak disparagingly about a patient.

Modifying the internal culture of a health center so it better reinforces the values medical educators wish to impart is no small task. The managed care revolution has caused medical schools and teaching hospitals to become increasingly less friendly to patients and students. The imperative to see large numbers of patients quickly has diminished personal contact between faculty and students., contributed to deterioration of bedside clinical skills, demoralized many faculty, and possibly had a deleterious impact on the quality of care.

The remedy involves working to make the internal culture of academic health centers less commercial and more service oriented — a large task not easily accomplished.

There is reason to hope that the task can be achieved, provided medical leaders have the courage to address the structural problems confronting medical education and practice and are willing to stand up for the interests of patients and the public.

JAMA September 1, 1999; 282: 881-82 Editorial by Kenneth M Ludmerer, Washington University, St Louis, MO

Comment:

If the role-modeling teacher cannot relate empathetically to all of the many patients she has to see in one day, it is possible to connect empathetically with at least one. A partial loaf is better than none. Students may then learn and retain most valuable lessons from one encounter. RTJ

See also:

- 1 "Teaching Professionalism in Undergraduate Medical Education" JAMA September 1, 1999; 282: 830-32
- 2 "Mindful Practice" JAMA September 1, 1999; 282; 833-39

Read the Original !

9-18 GAINING INFORMED CONSENT FOR SCREENING

"By offering screening to 250 000 we have helped a few, harmed thousands, disappointed many, used 1.5 million pounds each year, and kept a few lawyers in work" This is a conclusion by one of the authors of a report on cervical screening in Bristol, UK.

Screening has harms as well as benefits. Thus patients who undergo screening should be made fully aware of both. Yet there are many barriers to seeking truly informed consent, and we know surprisingly little about effective ways of doing so.

The detrimental side effects of screening include anxiety, false alarms, false reassurance, unnecessary biopsies, overdiagnosis, and overtreatment. Some screening tests will detect a disease before some patient otherwise would have known about it, yet they go on to die of the disease at the same time they would have died if the screening had not been done. This just prolongs the time the patient is aware of the disease. (So called lead time. Eg, a patient develops a disease in January. It remains asymptomatic until July. The patient dies in December. Treatment is ineffective whether given in January or July. The lead time is six months.)

False positive tests can cause major distress and prompt further investigation, often invasive, before the patient can be cleared.

There are misconceptions among the public about the purpose of screening and the accuracy of screening tests. When applied to a population, screening can be complex, of limited effectiveness, and expensive.

"Because of the combination of benefit and harm in all procedures, the individuals being screened must receive full and accurate information about the procedure and must give their informed consent." "Failure to obtain informed consent for many current preventive interventions is clearly unethical."

But it is not clear what information should be given, how much information should be given, and how this should be framed.

Guidelines on seeking consent include:

1. The purpose of the screen
2. The likelihood of positive and negative findings
3. The possibility of false positives
4. Uncertainties and risks attached to the screening process
5. Any significant medical, social, or financial implications of screening for the particular condition
6. Follow-up plans, including availability of counseling and support services

Many impediments exist to obtaining such consent. Time is a universally limiting factor. The information is complex. Many patients find it difficult to assimilate the information. (Including illiterate patients.)

"Above all, we need to respect patients' autonomy — and that includes their right to decide not to undergo a screening intervention, even when refusal may result in harm to themselves."

BMJ September 18, 1999; 319: 722-23 Editorial by Joan Austoker, Department of Primary Care, Oxford University, UK

Comment:

Screening is defined as testing for a disease in patients who have no symptoms or signs of that disease.

I know that many primary care clinicians automatically perform screening without forethought, and without informing the patient. (Eg, automatically ordering a PSA in older men.)

Clinicians should have a method of quickly determining a patient's views on screening. How to inform them of the risks as well as benefits remains a difficult task, and an important aspect of the art of medicine. I suspect some clinicians respect the pitfalls of screening and are able to discern which individual patient might wish to consider screening, and be concerned about imparting pre-screening information to the patient. (Perhaps aided by written information.) Patients should be provided with all the information they want. Some do not want any.

I know busy clinicians will feel strongly that this is an impossible task, given an overwhelming number of patients, and limited time and funding.

The task will never be completely satisfied. But, I believe the complete clinician will be ever mindful of the problem.

A recent article suggested we should calculate the number needed to screen as a complement to the number needed to treat. This gives an indication of the effectiveness of the screen. RTJ
