PRACTICAL POINTERS

FOR

PRIMARY CARE

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HIGHLIGHTS MAY 2001

5-1 EXECUTIVE SUMMARY OF THE THIRD REPORT OF THE NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) EXPERT PANEL ON DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS (Adult Treatment Panel III)

Practical point: All primary care clinicians should have a copy of these guidelines available for reference and distribution to patients with lipid problems. This will include millions.

5-2 PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

Type 2 diabetes can be prevented by changes in the lifestyle of patients with impaired glucose tolerance

Although the average amount of weight lost was not large, the difference between groups in incidence of diabetes was substantial. Even a relatively small loss of 5% of weight was important. The conservative target of more than 4 hours of exercise per week was associated with a significant reduction in risk. "The reasonably low dropout rate in our study indicates that subjects with impaired glucose tolerance are willing and able to participate in a demanding intervention program."

Practical point: This is an important study. Glucose metabolism should be checked in older patients. Discovery of moderate abnormalities (impaired fasting glucose and impaired glucose tolerance) will provide an excellent opportunity to encourage patients to modify their lifestyles. RTJ

5-3 IS THE PLACEBO POWERLESS?

An Analysis of Clinical Trials Comparing Placebo with No Treatment

This investigation concludes that placebo response represents a regression of symptoms to the mean and not a true therapeutic effect.

Practical point: Primary care clinicians must decide whether to 1) accept the possibility that placebos do indeed have a beneficial effect some times, for some patients. or 2) to believe they have no beneficial effect whatsoever, and avoid their use. Most clinicians will still tilt toward 1).

5-4 ENDOGENOUS OPIOIDS, PLACEBO RESPONSE, AND PAIN

It was suggested as early as 1978 that the analgesic response to placebo is mediated by endogenous opioids. Well designed studies have shown clearly that the placebo response to pain exists and that endogenous opioids have an important role in its mediation.

Practical point: The placebo response is physiological and mediated by endogenous opioids – a system which can provide pain relief. It is wrong to assume, as many clinicians still do, that a placebo response represents imagined pain or malingering.

5-5 MEDICAL TREATMENT OF PERIPHERAL ARTERIAL DISEASE AND CLAUDICATION

Peripheral atherosclerotic disease is an important manifestation of systemic atherosclerosis. It carries the same relative risk of death from cardiovascular disease as does a history of coronary heart disease or cerebrovascular disease.

Practical point; Patients with PAD should be candidates for secondary prevention strategies, including aggressive risk factor modification and antiplatelet drug therapy. Most patients are undertreated. The FDA has approved cilostazol (*Pletal*) for treatment of claudication. It inhibits platelet aggregation, arterial thrombus formation, and vascular smooth-muscle proliferation, and causes vasodilation.

5-6 EFFECT OF CARVEDILOL ON OUTCOME AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: THE CAPRICORN RANDOMISED TRIAL.

In patients treated long-term after an acute MI complicated by left ventricular systolic dysfunction. carvedilol,a beta-blocker, started within days after the MI, was associated with reduction in all-cause and cardiovascular mortality, and recurrent non-fatal MI. Benefits were in addition to aspirin and ACE inhibitors.

Practical point: Primary care clinicians will be following more patients taking beta-blockers. Starting low and going slow is a critical clinical application.

5-7 EXPANDING INDICATIONS FOR BETA-BLOCKERS IN HEART FAILURE

It is now clear that the interaction between the adrenergic nervous system and the failing heart is more complex than first realized. Chronic overexposure of the heart to norepinephrine causes hypertrophy, ischemia, and myocyte damage. The theory that the adrenergic system has a maladaptive role in chronic HF is supported by the salutary effects of beta-blockade on clinical outcomes demonstrated by large clinical trials.

Practical point: Beta-blockers represent an advance in the treatment of HF. They appear to be effective in patients with a wide spectrum of systolic HF — mild to severe.

These drugs must be administered cautiously and the dose escalated slowly in all patients with HF.

5-8 BENEFITS OF PRAVASTATIN ON CARDIOVASCULAR EVENTS AND MORTALITY IN OLDER PATIENTS WITH CORONARY HEART DISEASE ARE EQUAL TO OR EXCEED THOSE SEEN IN YOUNGER PATIENTS: The LIPID Trial

Practical point: Older persons with established coronary disease and average or moderately elevated cholesterol levels may benefit from secondary prevention with pravastatin therapy. Co-morbidity, expected length of life, and personal preference are contraindications, not age.

5-9 PROSTATE-SPECIFIC-ANTIGEN TESTING FOR EARLY DETECTION OF PROSTATE CANCER

PSA testing does detect PC at an early age in many cases. However, at present, data are not available from large, well-designed, randomized trials to determine whether early detection is beneficial, harmful, or has no effects. As a result, the optimal strategy remains unknown.

A discussion about testing should include: the likelihood that PC will be diagnosed; the possibility of false positive and false negative tests; the anxiety associated with a positive test; and the uncertainty regarding whether screening reduces the risk of death from PC. Randomized trials have indicated that routinely providing such information reduces the proportion of men who elect to be tested, although many still elect to do so.

Practical point: Primary care clinicians should not automatically order a PSA screen on their male patients over age 50. They should first make sure the patient has enough understanding of adverse effects of possible follow-up procedures and surgery (or radiation) in order to make an informed decision about screening.

5-10 CURRENT APPROACHES TO CERVICAL-CANCER SCREENING

Although screening saves lives, there is no consensus about when screening should start, how long it should continue, the frequency of screening, or the optimal screening technique. Information needed to make informed decisions is, in many respects, incomplete. The article offers suggestions and guidelines.

5-11 AUTOMATED SPHYGMOMANOMETRY: AMBULATORY BLOOD PRESSURE MEASUREMENT

Practical point: Due to the frequent occurrence of difficult-to-treat hypertension, all primary care practices should have some method of measuring ambulatory BP

5-12 WHAT TO DO WHEN BLOOD PRESSURE IS DIFFICULT TO CONTROL

In the majority of patients treated for hypertension, target BP levels are not achieved.Practical point: Primary care clinicians should consult a check-list of the reasons for inadequate control.

5-13 ROUTINE HOME TREATMENT OF DEEP VEIN THROMBOSIS

A study in this issue of BMJ adds to the growing evidence supporting the safety and feasibility of home treatment for acute DVT. The investigators concluded that most outpatients presenting with acute DVT can be treated at home. Admission to hospital is required mainly due to infrastructure problems, rather than for medical reasons.

Practical point: Some primary care clinicians may be able to arrange home care. It requires adequate resources.

5-14 MENINGOCOCCAL DISEASE

A review. Smoking and inhaling smoke may predispose to meningococcemia.

Practical point: Primary care clinicians should be prepared to administer antibiotics empirically to sick patients suspected of meningococcemia. Delay increases mortality.

5-15 MANAGEMENT OF CHRONIC TENSION-TYPE HEADACHE WITH TRICYCLIC ANTIDEPRESSANT MEDICATION, STRESS MANAGEMENT THERAPY, AND THEIR COMBINATION

Practical point: Antidepressant medication and stress management therapy were each modestly effective in treating chronic tension-type headache. Combined therapy may be more beneficial.

5-16 RANDOMISED CROSSOVER TRIAL OF TRANSDERMAL FENTANYL AND SUSTAINED RELEASE ORAL MORPHINE FOR TREATING NON-CANCER PAIN

Patients with chronic non-cancer pain preferred transdermal fentanyl over oral sustained release morphine. Fentanyl provided better pain relief with less constipation, and an enhanced quality of life.

Practical point: Primary care clinicians must be able to provide adequate pain relief to patients with chronic pain, especially terminal patients. Fentanyl may be a good choice.

5-17 OPIOIDS IN CHRONIC NON-MALIGNANT PAIN

"The use of opioids in chronic non-malignant pain is profoundly messy. A simple start is to say that if somebody has severe pain which responds to opioids, and for which there is no other effective remedy, then why should they not receive opioids?" Two judgements are then implicit: 1) that opioids are effective, and 2) that other remedies are not.

"There is no evidence base on which we can rely other than common sense, our own experience, and that of others."

Practical point: A trial of opioids beckons only when the many other conventional pain treatments have been tried. It should not be withheld for fear of addiction in sick patients with chronic pain.

5- 18 ORAL MUCOLYTIC DRUGS

Practical Point: A trial of oral mucolytics may be worthwhile in patients with severe COPD.

5-19 EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

Practical point: Primary care clinicians should be aware of this possibly beneficial advance. Look for general release and further information.

5-20 MICROBUBBLE CONTRAST AGENTS: A New Era in Ultrasound

Until recently, contrast agents had little place in ultrasonography. This has changed with the introduction of microbubbles— small (typically 3 um in diameter, gas filled bubbles that are usually given intravenously). Injecting a gas into the circulation may seem potentially hazardous, but extensive clinical experience has shown that the tiny volume of air or gas given (under 200 uL) is not dangerous.

Microbubbles work by resonating in an ultrasound beam, rapidly contracting and expanding in response to the pressure changes of the sound wave. They vibrate strongly at the high frequencies used for diagnostic ultrasound. This makes them several thousand times more reflective than normal body tissues.

Powerful applications are emerging.

5-21 RACIAL PROFILING IN MEDICAL RESEARCH

This editorialist maintains that attributing differences in a biological endpoint to race is not only imprecise, but also of no proven value in treating an individual patient.

Race is a social construct, not a scientific classification.

Sadly, the idea of race remains ingrained in clinical medicine. On ward rounds, it is routine to refer to a patient as “black”, “white”, or “Hispanic”. Yet these vague epithets lack medical relevance.

Practical point: The editorialist has a valid moral point, but not a practical clinical application. Race still plays an important role in determining pretest probabilities.

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REFERENCE ARTICLE

5-1 EXECUTIVE SUMMARY OF THE THIRD REPORT OF THE NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) EXPERT PANEL ON DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS (Adult Treatment Panel III)

(*This is an update on recommendations for clinical management. It is a basic guideline for patients, most of whom need some of the advice. I abstracted important highlights. RTJ*)

Screening:

All adults over age 20 should have a lipid profile done every 5 years.

A complete lipid profile should be used at least as the initial test

The goals:

LDL-cholesterol -- optimal under 100 mg/dL

Total cholesterol -- optimal under 200

HDL-cholesterol --- optimal over 40

Triglycerides --- optimal under 150

(Elevated LDL-cholesterol remains the primary goal of therapy. HDL-c is also a target.)

(Using total-c as the only determinant, or including total-c in the profile can mislead and confuse patients. It does not account for the HDL-c component. There is a great difference in risk between 1) a woman with a total-c of 220 and a HDL-c of 70 [non-HDL-c = 150], and 2) a man with a total-c of 220 and a HDL-c of 30 [non-HDL-c = 190]. I believe total-c is included mainly because of tradition. It could be removed from the report. RTJ)

Focus on risk factors:

1. Use Framingham projections of the 10-year absolute risk of coronary heart disease (**CHD**) to identify patients for more intensive treatment.
2. Clinical atherosclerotic disease: symptomatic carotid artery disease, peripheral artery disease, abdominal aortic aneurysm.
3. Patients with diabetes (without CHD) are raised to the same risk category as patients with established CHD. Most have multiple risk factors.
4. Identify patients with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle.
5. Consider the metabolic syndrome as a constellation of risk factors:

   Abdominal obesity: (waist circumference: men-- > 40 in; women >35 in [1]

   Elevated triglyceride: > 150 mg/dL

   Low HDL-cholesterol: < 40 for men; < 50 for women

   Raised BP: > 130/85

   Fasting glucose: > 110 mg/dL

6. Consider other major risk factors as increasing risk and requiring attention:

   Cigarette smoking

Hypertension (> 140/90)

Family history of premature CHD

Age : men > 45; women > 55

Support for implementation

1. Complete lipoprotein profile as initial test. (Ie, fasting)
2. Encourage use of plant stanols and sterols and soluble fiber to enhance lowering of LDL-cholesterol
3. Recommends treatment beyond LDL lowering for patients with triglycerides >200 (When treating high triglycerides, the primary objective is still to reach the LDL-c goal. Exercise and weight loss are essential components of triglyceride-lowering therapy.)

Treatment:

Lifestyle changes:

Diet:

25% to 35% of calories as fat

Saturated fat < 7% of calories Polyunsaturated fat < 10% of calories

Monounsaturated fat < 20% Cholesterol < 200 mg

Increase soluble fiber intake up to 25 g daily

Add plant sterols and stanols 2 g/d

Weight management

Increase physical activity

Drug therapy:

Consider lipid-modifying drugs (mainly statins)

Risk category	LDL level to consider drug therapy
0 to 1 risk factor	160
2 or more risk factors	
10 year risk 10-20%	130
10 year risk < 10%	160
10-year risk > 20%	130

(The higher the risk, the lower the goal for LDL-c)

Aspirin for established CHD

JAMA May 16, 2001; 285: 2486-97 Publication NY the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda MD. **www.jama.com**

Comment:

1 This is interesting. The panel substitutes abdominal obesity for body mass index.

The guidelines will substantially increase costs and use of lipid-controlling drugs. Some suggest drug use will triple if guidelines are strictly followed. Strict implementation would make us a nation of statin drug takers.

A quick desk reference, including the Framingham estimates of 10-year risk, can be obtained from the NHLBI **http://www.nhlbi.nih.gov/guidelines/cholesterol/profmats.htm**

Risk is based on age, total cholesterol, smoking, HDL-cholesterol, and systolic BP.

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5-2 PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

Modifiable risk factors such as obesity and physical inactivity are the main non-genetic determinants of type 2 diabetes.

Impaired glucose tolerance is an intermediate category between normal glucose tolerance and overt diabetes. It can be determined by the oral glucose tolerance test (**OGTT**) Persons with impaired glucose tolerance (2h post 75 g glucose challenge = 140 to 200) are at increased risk of developing type 2 diabetes. They are an important target group for interventions aimed at preventing diabetes.

This study asked --Can type 2 diabetes be prevented by interventions that affect the lifestyles of persons at high risk?

Conclusion: Lifestyle interventions can prevent development of type 2 diabetes.

STUDY

1. Followed over 500 middle-aged (mean age 55), overweight persons (mean BMI = 31). All had impaired glucose tolerance -- plasma glucose 140 to 200 2 hours after 75 g glucose challenge).[1]
   Mean fasting glucose = 110; mean 2-h glucose = 159.
2. Randomized to: 1) individualized counseling aimed at reducing weight, reducing intake of total fat and saturated fat, increasing intake of fiber, and increasing fitness, or 2) control group.
3. Performed an OGTT annually. The diagnosis of diabetes was confirmed by a second test.
4. Mean duration of follow-up = 3.2 years.

RESULTS

1. Mean weight loss between baseline and end of 1 year = 4.2 kg in the treatment group and 0.8 kg in the control group. Mean fasting glucose in the intervention group at 1 year declined by a mean of 4 mg/dL; 2-hour post glucose challenge declined by a mean of 15 mg/dL.
2. Cumulative incidence of diabetes after 4 years = 11% vs 23%.
3. The reduction in the incidence of diabetes was directly associated with changes in lifestyle.
4. At 4 years, 10% of treatment group had developed diabetes vs 21% % of controls.
   (Absolute difference = 11% ; NNT for 4 years with lifestyle changes to prevent development of one case of diabetes = 9)

DISCUSSION

1. Type 2 diabetes can be prevented by changes in lifestyle of individuals at high risk for diabetes.
2. The preventive effect of the intervention was most pronounced among subjects who made comprehensive changes in lifestyle.
3. Although the average amount of weight lost was not large, the difference between groups in incidence of diabetes was substantial. Even a relatively small loss of 5% of weight was important.
4. The conservative target of more than 4 hours of exercise per week was associated with a significant reduction in risk.
5. "The reasonably low dropout rate in our study indicates that subjects with impaired glucose tolerance are willing and able to participate in a demanding intervention program."

CONCLUSION

Type 2 diabetes can be prevented by changes in the lifestyle of patients with impaired glucose tolerance

NEJM May 3, 2001; 344: 1343-50 Original investigation by the Finnish Diabetes Prevention Study Group, first author Jakko Tuomilehto, National Public Health Institute, Helsinki. www.nejm.org

Comment:

1 The WHO 1985 diagnostic criteria were used to define impaired glucose tolerance (**GT**) and diabetes:

A. Impaired GT = fasting plasma glucose less than 140 mg/dL and a 2-hour post 75 gm plasma glucose between 140 and 200

B. Diabetes = either a fasting plasma glucose 140 or over, or 2 hour post 75 g glucose challenge over 200, or both.

Note these are the 1985 WHO standards. In 1999, the WHO changed the levels from 140 to 126:

A. Impaired GT = fasting glucose less than 126, and a 2 hour post challenge glucose 140 to 200.

B. Diabetes = fasting glucose 126 or over, or 2 hour post challenge glucose over 200 (or both).

Individuals with impaired glucose tolerance are at very high risk of developing diabetes ñ an estimated 33% over 6 years. Individuals with impaired fasting glucose (110 to 125) also have about a 33% chance of developing diabetes. Patients with both impaired fasting glucose and impaired glucose tolerance have about a 66% chance.

These interventions would be even more beneficial to prevent onset of impaired glucose tolerance RTJ

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5-3 IS THE PLACEBO POWERLESS?

An Analysis of Clinical Trials Comparing Placebo with No Treatment

"Placebos have been reported to improve subjective and objective outcomes in up to 30 to 40 percent of patients with a wide range of clinical conditions." An article published in 1955 [1] suggested that placebos have a high degree of therapeutic effectiveness in treating subjective responses. This was interpreted as a real therapeutic effect. The 35% figure has often been cited as evidence that a placebo can be an important medical treatment.

The quality of the evidence supporting this finding has not been rigorously evaluated. The vast majority of reports from randomized trials have estimated the effect of placebos as the difference from baseline in the condition of patients in the placebo group compared with those in the active treatment group. The effect of placebo cannot, therefore, be distinguished from the natural course of the disease or regression to the mean.[2]

These investigators suggest that a more accurate determination of the placebo effect could be assessed by comparing placebos with no treatment.

Conclusion: There was little evidence that placebos have a powerful clinical effect.

STUDY

1. A systematic review identified 114 clinical trials in which patients were randomized to either 1) placebo or 2) no treatment. Considered 40 different clinical conditions - eg, hypertension, asthma, anemia, hyperglycemia, hypercholesterolemia, alcohol abuse, smoking, obesity, common cold, pain, and others.
   A. 32 trials (over 3700 patients) had binary outcomes ie, reported relative risks of outcomes – placebo vs no treatment
   B. 82 trials (over 4700 patients). reported continuous outcomes (ie, effect of placebos vs no treatment on a sliding scale -- eg, 0 to 100).
2. A placebo could be pharmacologic (eg, a tablet typically lactose); physical (eg, a manipulation -sham transcutaneous electrical nerve stimulation, machine turned on or off); or psychological (eg, a conversation , non-directional).

RESULTS

1. Binary outcomes: Compared with no treatment, placebo had *no* effect on binary outcomes, regardless of whether outcomes were subjective or objective.
2. Continuous outcomes: Placebo had a beneficial effect, but the effect decreased with sample size, possibly indicating bias of the smaller trials. The pooled mean difference was significant for the trials with subjective outcomes, but not for those with objective outcomes. In 27 trials involving treatment of pain, placebo had a beneficial effect -- a reduction in intensity of pain by 6 mm on a 100 mm visual analogue scale.

DISCUSSION

1. "Placebo" is difficult to define. Generally, they are control treatments with similar appearance to the

study treatment, but without any specific activity.

2. The investigators admit several types of bias may have affected their findings. Blinding was not possible. Patients in the no-treatment groups would know they were not treated; those in the placebo groups would think they had received treatment.

CONCLUSION

"We found little evidence that placebos, in general, have powerful clinical effects, aside from possible small benefits in studies with continuous subjective outcomes, and for treatment of pain."

"Outside the setting of clinical trials, there is no justification for the use of placebos."

NEJM May 24, 2001; 244: 1594-602 Original investigation by Asbjorn Hrobjartsson, and Peter Gotzsche, University of Copenhagen, Denmark **www.nejm.com**

1 HK Beecher "The Powerful Placebo" JAMA 1955; 159: 1602-05

2 Regression to the mean: The tendency for random increases or decreases to occur and be closer to the mean as more observations are made. "If, for a symmetrical population with a single mode, a measurement, selected because it is extreme, is repeated, on average, the second reading will be closer to the mean than the first." An editorial in this issue comments: "The patient who has had a bad day with cancer or emphysema or a headache does not need a placebo to feel better the next day."

Comment:

Patients with chronic illnesses differ from those with acute illnesses. Their symptoms remain constant. They do not vary much from day to day. Individual patients with chronic illnesses whose symptoms are stable, cannot be said to regress to the mean. They are already at their symptom mean. Those who do respond to placebo treatment may indeed have a placebo response.

The investigators did find small but clinically useful benefits from placebo. Of course, clinicians do not use placebos to treat hypertension, asthma, or diabetes. For the many patients whose symptoms are nebulous, and who demand a prescription, I believe a placebo given with the comment ó "this might help" is ethical and not deceptive, provided the content of the placebo is known and standardized, and it is certain that it is not harmful in any way. I believe also that many drugs which are indeed active against some diseases are prescribed by clinicians who know they will not be active against the presenting complaint. (eg, overuse of antibiotics.) This is really placebo prescription.

Much of any putative power of placebos depends, not on the power of the lactose, but on the power of the practitioner who prescribes it. A caring, enthusiastic approach will enhance benefit. The power also depends on the patient who receives the placebo. Take a group of 1000 patients given placebo: 1) half take it regularly and enthusiastically; 2) half are non-compliant. Outcomes in group 1) will be better than those in group 2).

Differences in the approach of practitioners, and differences in the mind-set of patients, I believe, explain much of the effects of alternative medicine.

I doubt the study will convince many primary care clinicians to discontinue judicious use of placebos. I am not ready to dismiss the power of placebos. (*See the following abstract.)*

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5-4 ENDOGENOUS OPIOIDS, PLACEBO RESPONSE, AND PAIN

There is a large variability between individual patients in their response to analgesics. The subjective nature of pain varies between individuals.

The fundamental importance of the endogenous opioid system in pain and analgesia was realized over 20 years ago. The distribution of opioid receptors in the brain is well known. It may be possible to discover opioids diminish the perception of pain without simultaneously depressing respiration. This is the Holy Grail of analgesic pharmacology.

It was suggested as early as 1978 that the analgesic response to placebo is mediated by endogenous opioids. Well designed studies have shown clearly that the placebo response to pain exists and that endogenous opioids have an important role in its mediation.

There are 2 important clinical implications:

1) The placebo response is physiological and mediated by endogenous opioids, a system which can provide pain relief. It is wrong to assume, as many clinicians still do, that a placebo response represents imagined pain or malingering.
2) There should be more investigations into the role of placebo, not as a confounding factor interfering with study design, but as a method of enhancing the efficacy of, and reducing the variable response to analgesics and other methods of pain control.

However, there is no place for use of placebo alone in the management of pain.

Lancet June 16, 2001; 357: 1901-02 Editorial by David J Rowbotham, Leicester Warwick Medical School, Leicester, UK www.thelancet.com

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REFERENCE ARTICLE

5-5 MEDICAL TREATMENT OF PERIPHERAL ARTERIAL DISEASE AND CLAUDICATION

(This is an excellent review article. I abstracted some highlights I considered clinically important, as well as some I did not know, or had forgotten. I especially enjoyed the illustration of the ankle-brachial index on p 1610. RTJ)

Peripheral atherosclerotic disease **(PAD)** is an important manifestation of systemic atherosclerosis. It carries the same relative risk of death from cardiovascular disease as does a history of coronary heart disease or cerebrovascular disease. It is associated with increased risk of myocardial infarction, ischemic stroke, and death. Risk is elevated even in asymptomatic patients. The lower the ankle-brachial index, the greater the risk.

Major risk factors -- age; smoking; and diabetes. Other important risk factors -- hyperlipidemia; hypertension; and hyperhomocysteinemia.

Patients with PAD should be candidates for secondary prevention strategies, including aggressive risk factor modification and antiplatelet drug therapy. Most patients are undertreated.

Modification of risk factors and secondary prevention measures include:

Smoking cessation

LDL-cholesterol < 100mg/dL

Glycosylated hemoglobin < 7%

Blood pressure < 130/85

Angiotensin-converting enzyme inhibition

Antiplatelets: Aspirin or clopidogrel (*Plavix*)

Non-pharmacologic treatment includes supervised exercise therapy.

Drug therapy for claudication:

The FDA has approved cilostazol (*Pletal*) for treatment of claudication. It inhibits platelet aggregation, arterial thrombus formation, and vascular smooth-muscle proliferation, and causes vasodilation. It is a phosphodiesterase inhibitor similar to milrinone. (Milrinone was tried as an inotropic agent in treatment of heart failure, but led to an increase in mortality.) Although cilostazol has fewer cardiac effects, it should *not* be used in patients with heart failure. It can be administered with aspirin. There are no data on the safety of co-administration with clopidogrel.

NEJM May 24, 2001; 344: 1608-21 Review Article by William R Hyatt, University of Colorado School of Medicine, Denver. **www.nejm.org**

Comment:

Patients with PAD have reduced functional capacity limiting their ability to perform daily activities. Their quality of life is reduced. Treatment is rear-guard and limited in effectiveness. Primary prevention is effective and essential. We can do a great deal to reduce incidence of PAD -- just as much as we can to reduce incidence of coronary atherosclerosis. RTJ

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5-6 EFFECT OF CARVEDILOL ON OUTCOME AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION: THE CAPRICORN RANDOMISED TRIAL.

Several trials of angiotensin converting enzyme (**ACE**) inhibitors have conclusively shown substantial improvement in mortality and morbidity in patients with acute myocardial infarction (**MI**) who have confirmed left ventricular dysfunction or clinical heart failure.

Beta-blocker trials have also reported benefit in these patients. But, the trials were done in low-risk patients before use of thrombolysis, before introduction of ACE therapy, and before measurement of left ventricular function.

This study investigated the long-term efficacy of the beta-blocker carvedilol (*Coreg*) in patients with left ventricular dysfunction after an acute MI.

Conclusion: Post MI patients with left ventricular dysfunction benefited from carvedilol. Benefits were in addition to those of ACE inhibitors and aspirin.

STUDY

1. Multicenter, randomized, placebo-controlled trial entered over 1900 patients with acute MI. All had an ejection fraction less than 40% (mean = 33%) , with or without clinical heart failure.
2. Randomized 3 to 21 days after acute MI to: 1) carvedilol beginning at 6.25 mg twice daily and gradually increased as tolerated to a maximum of 25 mg twice daily, or 2) placebo.
3. Treatment of the index MI included nitrates, intravenous beta-blockers, heparin, diuretics, and thrombolysis or primary angioplasty. Almost all patients were taking ACE inhibitors and aspirin at randomization. These patients were being treated with the best evidence-based practice.
4. Follow-up = average of 1.3 years.

RESULTS

1. During the trial, about 20% of the patients withdrew permanently, and about 15% died.
2. All cause mortality was lower in the carvedilol group (12% vs 15%)
   [Absolute reduction = 3%; NNT(benefit one patient over 1.3 years) = 33].
3. Combined all-cause mortality and recurrent non-fatal MI = 14% vs 20%.
   [Absolute reduction 6%; NNT (benefit one patient over 1.3 years) = 17]

DISCUSSION

1. Carvedilol was started within days of an acute MI in patients with reduced cardiac output.
2. "The results of this study show substantial benefit from carvedilol with respect to major coronary events."
3. These patients were at particularly high risk. The acute phase of MI is an intrinsically unstable period, especially in patients with left ventricular dysfunction. About one third required intravenous diuretics during the acute event.
4. Based on previous studies, the investigators calculated the benefit at one year was in addition to any benefits from ACE inhibitors given alone.

CONCLUSION

In patients treated long term after an acute MI complicated by left ventricular systolic dysfunction, carvedilol was associated with a reduction in frequency of all-cause and cardiovascular mortality, and recurrent non-fatal MI. Benefits were in addition to aspirin and ACE inhibitors.

Lancet May 5, 2001; 357: 1385-90 original multicountry investigation by the "Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study **www.thelancet.com**

Comment:

Lancet considered this study important enough to fast-track.

The large number of deaths and withdrawals during the trial calls attention to the poor prognosis and the difficulty of treating these high-risk patients.

The investigation was careful to start carvedilol at a low dose and gradually increase. This required careful follow-up. RTJ

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5-7 EXPANDING INDICATIONS FOR BETA-BLOCKERS IN HEART FAILURE

(*This editorial comments and expands on the preceding article*.)

"For more than a century, clinicians have noted that tachycardia, cutaneous vasoconstriction, diaphoresis and reduced urinary output are cardinal manifestations of severe heart failure (**HF**) and surmised that these findings are caused by increased adrenergic activity. " Indeed, plasma norepinephrine concentrations are elevated in HF, while cardiac stores are reduced. Norepinephrine stimulates the failing myocardium (a positive inotropic effect). The resultant vasoconstriction helps maintain perfusion to vital organs.

This hypothesis was subsequently supported by the observation that short-term administration of beta-blockers sometimes causes a life-threatening intensification of HF in patients with severe forms of HF.

It is now clear that the interaction between the adrenergic nervous system and the failing heart is more complex than first realized. Chronic overexposure of the heart to norepinephrine causes hypertrophy, ischemia, and myocyte damage. The theory that the adrenergic system has a maladaptive role in chronic HF is supported by the salutary effects of beta-blockade on clinical outcomes demonstrated by large clinical trials.

Thus, thinking about beta-blockers and HF has made an 180 degree turn, at least in patients with moderate HF. In all trials, the blockers were administered orally in gradually escalating doses.

Now, in this issue of NEJM, a study reports the effects of beta-blockers in more severe HF.[1]

The carvedilol study enrolled patients with dyspnea or fatigue at rest or on minimal exertion and with left ventricular ejection fractions less than 25%. The trial was stopped early because of a significant beneficial effect on survival. Benefit was demonstrated even in those with ejection fractions of 15% or lower.

It is clear that beta-blockers represent an advance in the treatment of HF. They appear to be effective in patients with a wide spectrum of systolic HF ó mild to severe.

There are contraindications: reactive airway disease, sinus node dysfunction, and abnormalities of the cardiac conduction system.

These drugs must be administered cautiously and the dose escalated slowly in all patients with HF.

NEJM May 31, 2001; 344: 1711-12 Editorial by Eugene Braunwald, Brigham and Women's Hospital, Boston, Mass. **www.nejm.org**

1 "Effect of Carvedilol on Survival in Severe Chronic Heart Failure" NEJM May 31, 2001; 344: 1651-18. The article comments:

Carvedilol is a wide-spectrum beta-blocker (blocks alpha 1, beta-1, and beta-2 receptors). In this double-blind study carvedilol reduced risk of death by 35% over 11 months in patients with severe HF (mean age ó 63; ejection fraction ó20%). Initial dose was 3.125 mg twice daily, gradually increased every 2 weeks to 25 mg twice daily if tolerated. The drug was "well tolerated". In many patients it was given in addition to other drugs digitalis, diuretics, ACE inhibitors, spironolactone, amiodarone.

Carvedilol is not indicated in all patients with HF. Those requiring intensive care, those with marked fluid retention, symptomatic hypotension, and severe renal dysfunction were excluded. We should not assume that such patients would have favorable responses. It is possible that activation of the sympathetic nervous system is essential for maintenance of circulatory homeostasis in critically ill patients. If so, sympathetic inactivation may lead to rapid deterioration. Patients should first be stabilized, particularly in regard to their volume status. Primary care clinicians should seek consultation with an expert if possible.

Not all the benefit of carvedilol may be due to its beta-blocking action. Additional mechanisms, not fully understood may play a part. RTJ

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5-8 BENEFITS OF PRAVASTATIN ON CARDIOVASCULAR EVENTS AND MORTALITY IN OLDER PATIENTS WITH CORONARY HEART DISEASE ARE EQUAL TO OR EXCEED THOSE SEEN IN YOUNGER PATIENTS: The LIPID Trial

Statin drugs lower risk of coronary events in patients with moderately elevated cholesterol levels as well as in those with high levels,

This study assessed effect of pravastatin (*Pravachol*) as secondary prevention in patients with established coronary heart disease (**CHD**). It compared outcomes in patients over age 65 with those age 31 to 65.

Conclusion: In older patients (> 65) with CHD, and average or moderately elevated cholesterol levels, pravastatin was associated with reduced risk of all major cardiovascular events and all cause mortality. The absolute benefit was greater in older patients.

STUDY

1. Multicenter study randomized over 3500 patients age 65-75. All had a history of previous myocardial infarction (MI) or unstable angina.
2. Baseline total cholesterol levels ranged from 155 mg/dL to 271 mg/dL.
3. Randomized both older and younger patients to: 1) pravastatin 40 mg daily, or 2) placebo.
4. Follow-up = 6 years.

RESULTS

1. As expected, older patients were at greater risk than younger patients for death, recurrent MI, unstable angina, and stroke.

2. In the older age group (65+), mortality was reduced by 21%; death from CHD reduced by 24%; MI by 26%;

and stroke by 12% in the pravastatin group as compared with the placebo group

3. For every 1000 older patients treated over 6 years, pravastatin prevented 45 deaths, 33 MIs, 32 unstable angina events, 34 coronary revascularization procedures, and 13 strokes.

4. Pravastatin was well tolerated ó no significant difference in reported adverse effects compared with placebo.

DISCUSSION

1. In this cohort of high-risk older patients who previously had an MI, pravastatin was associated with a reduction in risk of major coronary events. (Secondary prevention)

2. The absolute reduction in risk was greater among older patients than among the young because of the greater risk for outcome events in the elderly. Over 6 years, 45 deaths and 47 major coronary events were prevented per 1000 older individuals vs 22 and 32 per 1000 in the younger age group.

3. The investigators believe that benefits of cholesterol-lowering therapy are so strong that drug therapy should be considered in all patients over age 65 with established coronary disease. (Secondary prevention)

CONCLUSION

In older persons with established coronary disease and average or moderately elevated cholesterol levels, secondary prevention with pravastatin therapy was associated with a reduction in all major cardiovascular events and all-cause mortality.

Annals Int Med May 15 2001, 134: 931-40 Original investigation by the LIPID investigators, first author David Hunt, Royal Melbourne Hospital, Parkville, Australia

www.annals.org

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5-9 PROSTATE-SPECIFIC-ANTIGEN TESTING FOR EARLY DETECTION OF PROSTATE CANCER

This article begins by asking about a 65-year old man who has no risk factors for prostate cancer (**PC**) except his age. Should a PSA be ordered?

After discussion the evidence, and reviewing guidelines, the author concludes:

PSA testing does detect PC at an early age in many cases. However, at present, data are not available from large, well-designed, randomized trials to determine whether early detection is beneficial, harmful, or has no effects. As a result, the optimal strategy remains unknown. Decision analysis suggests that, given certain assumptions, PSA screening could be cost effective, at least in younger men.

On the basis of available data, men who are 50 to 75 years of age (depending on general state of health) should be made aware of the availability of PSA and its potential benefits and harms. They then can make an informed choice about screening.

A discussion about testing should include: the likelihood that PC will be diagnosed; the possibility of false positive and false negative tests; the anxiety associated with a positive test; and the uncertainty regarding whether screening reduces the risk of death from PC. Randomized trials have indicated that routinely providing such information reduces the proportion of men who elect to be tested, although many still elect to do so.

Clinicians should not be dismayed by either choice.

NEJM May 3, 2001; 344: 1373-77 Review by Michael J Barry, Harvard Medical School, Boston Mass.
www.nejm.org

Comment:

This is the first of *Clinical Practice* a feature highlighting common clinical problems, citing evidence supporting various strategies and guidelines, and concluding with the author's clinical recommendations.

Regarding PSA screening, the evidence is equivocal. Giving the patient full information so he may make an informed choice, is an important clinical point. Clinicians often make the serious mistake of ordering a screening PSA routinely and informing the patient only after the result is returned.

At my age, I tell my primary care physician that I do not want a PSA done. I do not want to worry about it. RTJ

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REFERENCE ARTICLE

5-10 CURRENT APPROACHES TO CERVICAL-CANCER SCREENING

(I abstracted a few highlights. RTJ)

Dramatic reductions in the incidence of squamous cell cancer of the cervix have accompanied the wide-spread use of Pap tests in the US. All women who have a cervix and who are, or have been, sexually active are encouraged to participate in screening programs. "The Pap smear remains the archetype of a successful preventive intervention."

Cervical cancer is thought to be the long-delayed consequence of sexually transmitted human papilloma virus (HPV) infection.[1]

Although screening saves lives, there is no consensus about when screening should start, how long it should continue, the frequency of screening, or the optimal screening technique. Information needed to make informed decisions is, in many respects, incomplete. The article offers suggestions and guidelines:

1. Beginning screening: Most guidelines suggest either at age 18, or when the woman becomes sexually active.
2. Ending screening: Most authorities do not specify any specific age. Women over age 65 who

have undergone regular screening can discontinue if results have been consistently normal over the years.

3. Interval between screens: Interval can be extended to as long as 3 years if 2 or 3 consecutive tests have been normal. Annual examinations are recommended for high risk groups: first sexual intercourse younger than age 18; multiple partners or a consort with multiple partners; smoking; low socio-economic status; immunodeficiency. .
4. HPV testing: Newer methods of HPV detection have led to increasing interest in the role of testing for HPV. One of the most promising uses is to determine which women with low-grade cytologic abnormalities require colposcopic evaluation. HPV can help determine which women who have a single smear showing atypical squamous cells of undetermined significance (ASCUS) should undergo colposcopy. "At present, the role of HPV testing as an adjunct to, or substitute for, established and effective cytologic screening programs has not been evaluated adequately."
5. After hysterectomy: Women who have undergone total hysterectomy for reasons other than cervical neoplasia should no longer be screened.

NEJM May 24, 2001; 344: 1603-07 "Clinical Practice", first author George F Sawaya, University of California, San Francisco. **www.nejm.org**

Comment:

1 I would like to know if HPV is the only cause of cervical cancer. I doubt it.

This begins a NEJM feature highlighting common clinical problems. Evidence supporting various strategies is presented, followed by formal guidelines when they exist, and the authors' clinical recommendations. RTJ

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REFERENCE ARTICLE

5-11 AUTOMATED SPHYGMOMANOMETRY: AMBULATORY BLOOD PRESSURE MEASUREMENT

Recently, the accuracy of conventional Riva-Rocci/Korotkoff technique of BP measurement has been questioned. Efforts have been made to improve the technique with automated devices. Newer applications include repeated measurements using traditional techniques, self-measurement of BP at home, and ambulatory BP measurements.

This article discusses ambulatory BP measurement (**ABPM**): which monitor to buy (it must be validated independently); what type of ABPM service to set up in the clinician's office, or in a hospital service; and training requirements (the technique requires experience and training). Nurses can be trained to give excellent service. Clinical indications for measuring ABP, features of white coat hypertension, ABPM in the elderly, resistant hypertension, and ABPM to guide treatment are also discussed.

Tables present comments on using the monitor, instructions to patients, and ways in which the data is gathered and presented. The article provides illustrations of several examples of ambulatory BP measurements over 24 hours.

BMJ May 5, 2001; 322: 1110-14 "Clinical Review" first author Eoin O'Brien

www.bmj.com/cgi/content/full/322/7294/1110

Comment: ABPM is an important clinical application. All primary care practices should make it available.

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5-12 WHAT TO DO WHEN BLOOD PRESSURE IS DIFFICULT TO CONTROL

There is no universally accepted definition of blood pressure that is difficult to control, uncontrolled, resistant, or refractory. One US guideline defined resistant hypertension as BP that cannot be reduced to below 140/90 (below 160 for isolated systolic hypertension) in patients who are complying with adequate triple drug regimens in appropriate dosage.

Resistant BP is common ó in as many as 50% to 75% of patients being treated for hypertension, target BP levels are not achieved. Most patients require two or three drugs to achieve BP less than 150/85.

This article reviews many reasons for difficulty in control. The most common are: suboptimal treatment, non-adherence to prescription, white coat hypertension, co-existing conditions, use of antagonists that can increase BP, and secondary causes of hypertension. Dietary habits (eg, salt intake) and exercise patterns should be reviewed.

There are many antagonists that can increase BP, including alcohol (more than 14 g absolute alcohol daily) , NSAIDs, amphetamines and sympathomimetic agents, and oral contraceptives. (*See check list p 1230*)

Co-existing conditions that may increase BP or interfere with treatment include: alcohol abuse, anxiety disorders, hyperinsulinism with insulin resistance, obesity, pregnancy, sleep apnea, and smoking. (*See check list p 1231*)

The article presents an algorithm, a commonsense approach to evaluation of resistant hypertension. (*p 1231*).

If hypertension is still resistant, despite aggressive treatment, consider selective, sequential evaluation for secondary causes of hypertension, starting with relatively common conditions such as renovascular and renal parenchymal disease.

BMJ May 19, 2001; 322: 1229-32 "Clinical Review" by Jane E O'Rorke, and W Scott Richardson, University of Texas, San Antonio www.bmj.com/cgi/content/full/322/7296/1229

Comment:

I believe the term "inadequately treated" is more descriptive than "refractory" or "resistant".
This is an important clinical point. Optimal BP can be achieved in the great majority of patients. Seeking and eliminating causes of inadequate control of hypertension is a basic clinical responsibility. The article may be filed and consulted as a check list. RTJ

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5-13 ROUTINE HOME TREATMENT OF DEEP VEIN THROMBOSIS

The emergence of low-molecular-weight heparin (**LMWH**) as a safe, effective, and convenient treatment for deep vein thrombosis (**DVT**) has challenged the conventional treatment of DVT. Formerly treatment with heparin required admission to the hospital.

LMWH is at least as effective and safe as unfractionated heparin for the initial treatment of DVT. It is given subcutaneously in a fixed, weight-adjusted dose without the need for laboratory monitoring. This simplification allows home treatment of acute DVT.

How can we judge which patients to treat at home? Those with recurrent DVT, with pulmonary embolism, co-morbid conditions, and those with associated increased risks of bleeding would best be admitted. In addition, there are concerns about feasibility of administering LMWH and following the prothrombin time daily as warfarin treatment is continued.

A study in this issue of BMJ[1] adds to the growing evidence supporting the safety and feasibility of home treatment for acute DVT. (Defined as non-compressible deep veins on ultrasonography with symptoms present for less than 2 weeks) The investigators followed 117 consecutive patients. Treatment at home included lower limb compression stockings and warfarin aiming for an INR of 2.0 to 3.0. LMWH was continued until target INR was reached. Protimes were measured at home.

Of 117 patients, 92 (79%) were discharged home and not admitted at all. The rest were admitted because of massive leg swelling, increased risk of bleeding, severe pain, self injection of LMWH not possible, compliance with INR testing would be poor, or logistic problems.

On follow-up, 3 home treated patients developed recurrent DVT; 4 had minor bleeding. No pulmonary embolism or major bleeding occurred.

The investigators concluded that most outpatients presenting with acute DVT can be treated at home. Admission is required mainly due to infrastructure problems, rather than for medical reasons.

Home treatment requires adequate resources.

BMJ May 19, 2001: 1192-93 Editorial by John Eikelboom, and Ross Baker, Royal Perth Hospital, Perth, Australia. **www.bmj.com/cgi/content/full/322/7296/1192**

1 BMJ May 19, 2001; 322: 1212-13 "Eligibility for Home Treatment of Deep Vein Thrombosis: A Prospective Study" first author Thomas Schwarz, University Hospital, Dresden, Germany**.**
www.bmj.com/cgi/content/full/322/7296/1212

Comment:

If concerns about home monitoring are solved, this can be an important, convenient, and cost-saving method of therapy. RTJ

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REFERENCE ARTICLE

5-14 MENINGOCOCCAL DISEASE

(*This article is an up-to-date review. I highlighted some points which are new and clinically significant, and some which I had forgotten, or never knew. RTJ*)

Meningococcal disease remains a leading cause of bacterial meningitis and sepsis in the U.S. Short of abolishing tobacco use, which is thought to be responsible for almost one third of cases [1], routine vaccination of high-risk populations is likely to be the most effective public health strategy for controlling meningococcal disease.

Humans are the only natural reservoir of *N meningitidis*. The nasopharynx is the site from which meningococci are transmitted by aerosol or secretions to others. Meningococci overcome host defenses and attach to the surface of nonciliated columnar mucosal cells of the nasopharynx where they colonize. (Meningococci are diverse organisms and are usually commensal.) Five to 10 percent of adults are carriers. Most strains are not pathogenic. In most persons, carriage is an immunizing process, resulting in a protective antibody response. In a small number of persons the organism penetrates the mucosa and gains access to the blood stream.

Persons who lack antibody-dependent immune bactericidal activity are most susceptible to meningococcal disease. Military recruits and college freshmen who have detectable bactericidal antibodies frequently become carriers, but do not contract the disease. The acquisition of the infection depends on the chance that a person will encounter and acquire a virulent strain. In households where a case of meningococcal disease has occurred, the risk of invasive disease in family members is increased by a factor of 400 to 800. Active and passive exposure to tobacco smoke and concurrent viral infection of the upper respiratory tract increases the risk of meningococcal disease by diminishing the integrity of the mucosa which then loses its barrier effect.

Clinical manifestations are difficult to distinguish from those of more common, but less serious illnesses. Meningococcemia is characterized by an abrupt onset of fever, a petechial or purpuric rash (may be maculo-papular and blanchable at onset), often with hypotension, acute adrenal hemorrhage, and multiorgan failure. Meningeal infection occurs in about 50% of patients who have hematogenous spread. It is similar to other forms of acute purulent meningitis, with sudden onset of headache, fever, and neck stiffness.

Despite treatment with appropriate antibiotics, the overall mortality has remained relatively stable over the past 20 years.

A chronic form of meningoccemia can occur with prolonged intermittent fever, rash, arthralgia, and headache.

Diagnosis; Sensitivity of culture may be low, especially if antibiotics have been given beforehand. Gram stain of the cerebrospinal fluid (**CSF**) is still considered important for rapid identification. Non-culture methods using commercially available kits to detect polysaccharide antigen in the CSF may enhance

laboratory diagnosis. Polymerase-chain reaction analysis can detect serogroups, but are not commercially available in the U.S.

Treatment: Effective antibiotics should be given promptly.[2] Penicillin is still an effective drug, but in the U.S. is rarely used as initial therapy. Since the clinical presentation of other bacterial infections is similar to that of meningococcemia other antibiotics are used empirically, directed by epidemiologic information. Vancomycin, broad spectrum cephalosporins, ampicillin and chloramphenicol are effective therapy.

Control and prevention: In the U.S., prevention measures have made secondary cases rare. Household members, contacts in day care, and anyone directly exposed to an infected patients oral secretions should receive antibiotic prophylaxis as soon as possible. Do not wait for cultures of contacts. Rifampin, ciprofloxacin, and ceftriaxone effectively eliminate nasopharyngeal carriage. Penicillin does not. (*See table p 1385 for a schedule of chemoprophylactic antibiotics.)*

The quadrivalent vaccine (A, C, Y and W-135) is available in the U.S. It has good immunogenicity by inducing bactericidal antibodies. Vaccination is recommended for health care workers and freshman college students (especially those living in dormitories). An effective vaccine against serotype B will take another 5 years or so to become available.

NEJM May 3, 2001; 344: 1378-88 *Medical Progress*, review article, first author Nancy E Rosenstein, Centers for Disease Control and Prevention, Atlanta, GA **www.nejm.org**

Comment:

1 The adverse effect of smoking in this context was a new point to me. Any reduction in the protective mucosa of the pharynx can increase likelihood of meningococcemia.

2 Prompt treatment is essential. Meningococcemia is a true medical emergency. Primary care clinicians in the UK are encouraged to carry injectable penicillin in their bags and administer it in the home to patients who are ill and who are clinically suspected to have the possibility of meningococcemia. The important point, however, is promptness, not the type of antibiotic.

The newly available activated protein C may be of benefit in treating sepsis due to meningococcemia. Protein C is a vitamin-K dependent glycoprotein circulating in the plasma as an inactive zymogen. The coagulopathy of meningococcemia impairs protein C activation. Replacement can prevent death. RTJ

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5-15 MANAGEMENT OF CHRONIC TENSION-TYPE HEADACHE WITH TRICYCLIC ANTIDEPRESSANT MEDICATION, STRESS MANAGEMENT THERAPY, AND THEIR COMBINATION

The one year prevalence of chronic tension-type headache (**CTTH**) is about 3% for women and 1.5% for men. Many suffer headaches almost every day. Almost half report impairment in work performance. CTTH is a risk factor for overuse of analgesic medications and the development of analgesic abuse headaches.

Continuous headaches and frequent comorbid psychiatric or analgesic use problems often rend CTTH difficult to manage.

This study evaluated the clinical efficacy of behavioral and pharmacological therapies, singly and combined.

Conclusion: Antidepressant drugs, and stress management are each modestly effective. Combined therapy may be more effective.

STUDY

1. Randomized, placebo-controlled trial entered over 200 patients with CTTH (mean age 37). Mean frequency of HA = 26 headache days per month. About 25% had comorbid migraine. Patients with more severe and frequent migraine were excluded.
2. Randomized to; 1) tricyclic antidepressants amitriptyline (*Elavil*) up to 100 mg daily of nortriptyline (*Generic*) up to 75 mg daily, 2) stress management therapy (**SMT**: relaxation, cognitive behavior, biofeedback), 3) the two therapies combined, or 4) placebo alone
3. Doses of the antidepressants were started low and gradually increased.
4. Psychologist- or counselor-administered SMT was given in 3 one-hour clinic visits.
5. Follow-up = 6 months.

RESULTS

1. Tricyclic drugs, and SMT each produced larger reductions in headache activity than placebo. They also reduced analgesic use and headache-related disability.
2. Antidepressants yielded more rapid improvements.
3. Combined therapy produced a 50% reduction in headache index scores; SMT (38%); placebo (29%).
4. At 6 months, mean headache index scores, days of at least moderate pain, analgesic medication use, and headache disability scores had all decreased in the 3 active treatment groups compared with placebo alone.

   (*See figure 2 p 2212*). There was no great difference between the 3 active groups.

DISCUSSION

1. Antidepressants alone, and stress management alone, and the combination were effective in reducing CTTH, analgesic medication consumption, and headache-related disability.
2. Response to placebo over 6 months was nil.
3. However, only 1/3 of patients in the antidepressant-only group recorded substantial (> 50%) reductions in headache activity.
4. Some benefit was recorded from SMT alone, but there was a lag of several months. Response was good in only 1/3 of patients.
5. Almost 2/3 of patients treated with combined therapy showed clinically significant (>50%) reductions in headache index scores. But, no significant advantage for combined therapy on other outcome variables.

6. Withdrawals varied between 17% and 31% in the active treatment groups; about 50% in the placebo group.

CONCLUSION

Antidepressant medication and stress management therapy were each modestly effective in treating chronic tension-type headache. Combined therapy may be more beneficial.

JAMA May 2, 2001; 285: 2208-15 Original investigation, first author Kenneth A Holroyd, Ohio University, Athens, Ohio **www.jama.com**

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5-16 RANDOMISED CROSSOVER TRIAL OF TRANSDERMAL FENTANYL AND SUSTAINED RELEASE ORAL MORPHINE FOR TREATING NON-CANCER PAIN

"Pain is one of the commonest reasons for visiting a doctor and is often undertreated or mistreated, with patients going from doctor to doctor for relief and finally moving outside mainstream medicine in increasing numbers."

Opioids are the mainstay of cancer pain management. Survey data also confirms the efficacy of opioids in the treatment of chronic non-cancer pain, and finds that fears of addiction are not justified. Politics, prejudice, and continuing ignorance still impede optimum prescribing.

Morphine, usually in sustained release form, is the standard for treatment of chronic pain against which others are judged. Fentanyl, a lipid soluble synthetic opioid can be delivered in a transdermal controlled release formulation. It provides continuous, controlled delivery for up to 72 hours. It has been shown to relieve neuropathic pain that is relatively insensitive to morphine.

This study compared patients' preference for transdermal fentanyl vs sustained release oral morphine. It assessed pain control, quality of life, and adverse events.

Conclusion: Fentanyl was preferred. It provided better pain relief and an enhanced quality of life.

STUDY

1. Randomized, multicenter, open-label, cross-over trial entered over 250 patients with chronic non-cancer pain. Mean age = 50. All had pain (mean duration = 9 years[1]) which required continuous treatment with potent opioids. 75% completed the trial.
2. Pain was classified as nocioceptive (stimulation of intact nocioceptors by noxious stimuli), neuropathic, (disease or trauma of the nervous system), or combined.
3. Randomized to: 1) oral sustained release oral morphine (*MS Contin*) 10, 30, 60, 100, or 200 mg, or 2) fentanyl patches (*Durogesic*) releasing 25, 50, 75, or 100 ug per hour. Then crossed over.

RESULTS

1. 65% of patients preferred fentanyl; 28% preferred morphine; 7% had no preference.

2. Better pain relief was the main reason for preferring fentanyl. More patients in the fentanyl group considered
pain control to be "very good" or "good (35% vs 23%). Fentanyl was reported to be as effective in neuropathic pain as in nocioceptive pain.
3. In the investigator's opinion, global efficacy of fentanyl was good or very good in 58% of patients compared
with 33% of morphine patients.
4. Patients receiving fentanyl had, on average, higher quality of life scores.
5. Incidence of adverse events was similar in both groups, but more patients receiving morphine experienced constipation; 41% experienced mild to moderate cutaneous problems associated with the fentanyl patch. Overall about one quarter of patients considered their pain control poor or very poor with either treatment.[2]

DISCUSSION

1. Potent opioids can provide satisfactory pain relief for the difficult clinical problem of chronic non-cancer pain. Both morphine and fentanyl provided effective pain relief. But, patients generally preferred treatment with transdermal fentanyl.
2. Similar results have been observed in other studies of patients with cancer pain.
3. Individual dose titration is vital and allows for the variability in patients' response to different opioids.
4. This study used a pragmatic, clinical practice approach which the authors thought justified in the light of recent problems applying quality designs to clinical trials. The "explanatory" (evidence based) approach requires a placebo for comparison, whereas the "pragmatic" approach generally compares a new treatment with the best older treatment in clinical use for the particular clinical circumstances. Pragmatic outcome measures such as quality of life and patients' preference may ultimately provide a more accurate evaluation of treatment effects than pain measures alone.

CONCLUSION

Patients with chronic non-cancer pain preferred transdermal fentanyl over oral sustained release morphine. Fentanyl provided better pain relief with less constipation, and an enhanced quality of life.

BMJ May 12, 2001; 322: 1154-58 "Primary Care", original investigation, first author Laurie Allan, Northwick Park and St Mark's NHS Trust, Harrow, Middlesex, UK
www.bmj.com/cgi/content/full/322/7295/1154

1 Note these patients had long-term non-cancer pain. The study was conducted by pain specialists.

2 Another indication of the difficulty in treating chronic pain

Comment:

Although this study was presented under the heading of "Primary Care", I did not abstract it as a guide for primary care clinicians. Most of us are privileged to have pain specialists back us up.

Some primary care clinicians may, however, be responsible for adequate pain control in an occasional patient with chronic pain. The approach to non-cancer pain requires a greater degree of clinical judgement than cancer pain.

I abstracted the article mainly to point out the sea change in approach to both cancer and non-cancer pain which has occurred over the past few decades.

As usual, the patient is the judge. Primary care clinicians who care for patients with severe chronic pain should give the patient the opportunity to compare different analgesics. RTJ

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5-17 OPIOIDS IN CHRONIC NON-MALIGNANT PAIN

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

"The use of opioids in chronic non-malignant pain is profoundly messy. A simple start is to say that if somebody has severe pain which responds to opioids, and for which there is no other effective remedy, then why should they not receive opioids?"

Two judgements are then implicit: 1) that opioids are effective, and 2) that other remedies are not.

Opioids are often withheld to protect society, or to protect the patient. The society argument is that the medical availability of opioid increases street addiction. (But, there has never been any strong evidence that medical use increases street problems. The introduction of oral morphine in Sweden in the early 1980s was shown *not* to increase addiction.) "We know that if the opioid sensitive pain later resolves, opioids can be stopped without patients becoming addicts." The grey areas here are judgements about the patient's potential for addictive behavior, and about the opioid sensitivity of the pain. No tests exist to help with either judgement. "We fear scenarios such as patients with no identifiable cause for their back pain using escalating doses of 'minor' then 'major' opioids. This fear could lead to draconian guidelines and thoughtless legislation which restrict opioid use to the detriment of those with genuine need."

"In cancer pain we claim that tolerance, the need for increasing doses to achieve the same result, is rare." Patients stay on the same dose for months. "We need to admit that escalating doses in the absence of disease progression is a red flag in the management of non-cancer pain."

"Diagnosis is not always a problem (eg, phantom pain and postherpetic neuralgia), but with back pain or abdominal pain we often struggle." If we accept that opioids are a treatment option even in the absence of a precise diagnosis, then we need to know: 1) whether non-opioid treatments have been tried rationally,[1] and 2) how to measure their success or failure. A trial of opioids beckons only when the many other conventional pain treatments have been tried. "There is no evidence base on which we can rely other than common sense, our own experience, and that of others." Few would be uncomfortable with opioid use that allows an elderly patient with rheumatoid arthritis to sit without pain, but few would be comfortable prescribing strong opioids long term for a young person with back pain.

BMJ May 12, 2001; 322: 1134-35 Editorial by Henry McQuay, Churchill Hospital, Oxford, UK

www.bmj.com/cgi/content/full/322/7295/1134

1 Pain specialists have an advantage over primary care clinicians in applying non-opioid and opioid therapies and determining their effectiveness. We should refer these patients when possible. RTJ

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5-18 ORAL MUCOLYTIC DRUGS FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: Systematic Review

"At least half of smokers will develop chronic bronchitis. Up to 15% will develop limiting symptoms from chronic obstructive pulmonary disease". (**COPD**). These patients may experience recurrent exacerbations with worsening symptoms and greater volume or purulence of sputum. Although the exacerbations can be treated with antibiotics, it would be useful to have other treatments that reduce their frequency and duration

This systematic review assessed the effects of *oral* mucolytics in adults with stable chronic bronchitis and COPD. Mucolytics increase the expectoration of sputum by reducing its viscosity or hypersecretion. They are used with varying frequency in the Western world. Do they actually reduce the frequency of exacerbations or days of illness? Do they improve lung function?

Conclusion: Mucolytics reduced acute exacerbations and days of illness.

STUDY

1. Systematic (Cochrane) review of randomized controlled trials in outpatients abstracted data from 23 trials. All compared at least 2 months of regular oral mucolytics with placebo.
2. The article did not list the different preparations used. An accompanying editorial remarked that acetylcysteine was one of the most frequently used.

RESULTS

1. Mucolytic treatment was associated with a mean reduction on 0.8 exacerbations per patient per year.

Based on the annualized rate of exacerbations in the control subjects of 2.7 a year. This is a 29% reduction.

2. The number needed to treat for one subject to have no exacerbation in the study period = 6.
3. Days of illness and number of days that patients took antibiotics were reduced in the treated group.
4. No difference in lung function or in adverse effects.

DISCUSSION

1. Mucolytic drugs had a modest but significant benefit on exacerbation rates in patients with COPD and chronic bronchitis.
2. "Clinicians and patients will need to judge for themselves whether the reductions in exacerbation rate

and days of illness seen with mucolytic drugs are large enough to warrant daily treatment for at least 3 to 6 months a year."

3. Cost is a factor. Short course antibiotics are much less expensive.
4. Benefit may be greater in those who have more severe COPD, and in those who have more frequent severe exacerbations and require hospitalization.

CONCLUSION

In patients with chronic bronchitis and COPD, treatment with oral mucolytics was associated with a reduction in acute exacerbations and days of illness. As these drugs have to be taken long term, they could be most useful in patients who have repeated, prolonged, or severe exacerbations.

BMJ May 26, 2001; 322: 1271-74 Systematic review by Phillipa J Poole and Peter N Black, University of Auckland, New Zealand. www.bmj.com/cgi/content/full/322/7297/1271

Comment:

I found 2 mucolytics listed in my 2001 PDR: 1) guaifenesin (*Organidine NR)* and 2) acetylcysteine (*Generic*) RTJ

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5-19 EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

Treatments for osteoporosis now include estrogens, selective estrogen-receptor modulators (SERMs), bisphosphonates, calcitonin, and calcium and vitamin D. All of these reduce bone resorption and moderately increase bone density. Some reduce the risk of fracture, but none routinely restores bone mass or strength to normal. Treatments that stimulate bone formation may overcome these limitations.

Parathyroid hormone (**PH**) stimulates bone formation and resorption, can increase or decrease bone mass. This depends on the mode of administration. Continuous infusions or daily subcutaneous injections stimulate bone formation similarly, but have different effects of bone resorption and bone mass: 1) continuous infusions which result in a persistent elevation of serum PH lead to greater net bone resorption; 2) daily injections cause only transient increases in PH concentration.

PH or its amino-terminal fragments (eg, PH (1-34) and analogues prevent, or partially reverse bone loss in humans.

This study tested the hypothesis that once-daily injections of PH (1-31) would increase bone mass and protect against fractures in postmenopausal women.

Conclusion: Treatment of postmenopausal osteoporosis with PH 1-34 decreased the risk of fractures. And increased total bone mineral density.

STUDY

1. Randomly assigned over 1600 postmenopausal women (mean age 70). All had prior vertebral fractures

(Ie, a secondary prevention study.)

2. Randomized to: 1) daily 40 ug of PH 1-34 given subcutaneously, or 2) placebo.

3. Mean follow-up = 21 months.

RESULTS

1.	PH	Placebo
New vertebral fractures	4%	14%
New non-vertebral fractures	3%	6%

2. Change in bone mineral density: +13 more percentage points in the lumbar spine and +6 more percentage points in the femoral neck than placebo.

3. Adverse effects were minor (occasional nausea and headache).

4. Subcutaneous PH has the greatest effect during the first 4 to 6 hours. At this time mild hypercalcemia (defined as that exceeding 10.6 mg/dL ó most less than 11.2 mg/dL) occurred at least once in 28% of women. Mean 24-hour urinary calcium excretion increased slightly in the PH group, but did not exceed 300 mg/day.

DISCUSSION

1. Daily injections of 1-34 PH increased bone mineral density of the spine and reduced the risk of new vertebral fractures and non-vertebral fractures.

2. The clinical benefits of PH 1-34 reflect its ability to stimulate bone formation and thereby increase bone mass and strength.

CONCLUSION

Treatment of postmenopausal osteoporosis with once daily injection of the PH amino-terminal fragment 1-34 decreased risk of vertebral and non-vertebral fractures. It increased vertebral, non-vertebral, and total body bone mineral density.

NEJM May 10, 2001; 344: 1434-41 Original investigation, first author Robert M Neer, Harvard Medical School, Boston, Mass. **www.nejm.org**

Comment:

Obviously an initial study. More to come. The interest lies in the ability of PH to increase bone mineralization, not merely decrease absorption.

PH (1-34) will be clinically available later this year. Trade name *Forteo*.

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RECOMMENDED READING

"Science, Medicine and the Future", Clinical Review

5-20 MICROBUBBLE CONTRAST AGENTS: A New Era in Ultrasound

Until recently, contrast agents had little place in ultrasonography. This has changed with the introduction of microbubbles— small (typically 3 um in diameter, gas filled bubbles that are usually given intravenously). Injecting a gas into the circulation may seem potentially hazardous, but extensive clinical experience has shown that the tiny volume of air or gas given (under 200 uL) is not dangerous.

Powerful applications are emerging.

Microbubbles work by resonating in an ultrasound beam, rapidly contracting and expanding in response to the pressure changes of the sound wave. They vibrate strongly at the high frequencies used for diagnostic ultrasound. This makes them several thousand times more reflective than normal body tissues. In this way they enhance both grey scale images and flow-mediated Doppler signals. The latter signals from blood are increased in intensity for several minutes after injection. The effect can be prolonged by infusing the bubbles. They can improve a non-diagnostic Doppler examination by raising the intensity of weak signals. For example, they can improve detection of flow in the intracranial arteries by transcranial Doppler, where the skull greatly attenuates the ultrasound signal.

Micro bubbles can also be injected into body cavities, allowing simple functional tests to be performed. (Eg, diagnosing vesico-ureteral reflux in children by injecting the bubbles into the bladder.)

Other specific diagnostic applications include imaging the liver and heart. Microbubble contrast agents highlight the left ventricular cavity and make the blood-tissue boundary much clearer. This helps to assess regional abnormalities in wall motion, to estimate ejection fraction, and to detect thrombi.

An exciting possibility: microbubbles may eventually be used to deliver drugs to specific organs. by incorporating a drug in the bubble, then causing the bubble to "pop" at a specific site.

BMJ May 19, 2001; 322: 1222-25 "Clinical Review", first author Martin JK Blomley, Imperial College School of Medicine, London. **www.bmj.com/cgi/content/full/322/7296/1222**

Comment:

The article cites several internet resources on microbubbles.

They are being manufactured by several companies. "Levovist" is one trade name.

See also "Detection of Prostate Cancer with a Microbubble Ultrasound contrast Agent" Lancet June 9, 2001: 357: 1849-50

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5-21 RACIAL PROFILING IN MEDICAL RESEARCH

(*This editorial comments on two studies in this issue of NEJM*.)

Two articles in this issue of NEJM deal with the treatment of heart failure in white and black patients. **1, 2** One reports that enalapril (*Vasotec*) , an ACE inhibitor, is more effective in treatment of left ventricular

dysfunction in whites than in blacks. The second finds that the beta-blocker carvedilol *(Coreg*) provides similar benefits in whites and blacks. Both articles refer to "race", "racial groups", "racial differences", and "ethnic backgrounds", but offer no plausible biological justification for making such distinctions.

This editorialist maintains that attributing differences in a biological endpoint to race is not only imprecise, but also of no proven value in treating an individual patient.

Race is a social construct, not a scientific classification. The American Anthropological Association states:

> It has become clear that human populations are not unambiguous, clearly demarcated, biological distinct groups. Throughout history whenever different groups have come into contact, they have interbred. The continued sharing of genetic materials has maintained humankind as a single species. Any attempt to establish lines of division among biological populations is both arbitrary and subjective.

Recently, data from the 2000 U.S. census show that even self-identification of race can be problematic. The degree of multiracial identification underscores the heterogeneity of the U.S. population and the futility of using race as a biological marker.

Social perceptions of what a person is, or is not, influences the availability, delivery, and outcome of medical care. These perceptions apply with dismaying regularity to black people and other minorities. Lifestyle, socio-economic status, and personal beliefs are powerful influences on heath care. But these are matters of morality and culture, and we must clearly distinguish them from biological aspects of race – from the danger of attributing a therapeutic failure the patient's "race" instead of looking for the real reason.

Sadly, the idea of race remains ingrained in clinical medicine. On ward rounds, it is routine to refer to a patient as "black", "white", or "Hispanic". Yet these vague epithets lack medical relevance.

"Physicians everywhere must teach the immorality of racial discrimination in clinical practice."

Perhaps the first benefit of the Human Genome Project will be to lead us to the understanding that in medicine, there is only one race – the human race.

NEJM May 3, 2001; 344: 1392-93 Editorial by Robert S Schwartz, NEJM staff **www.nejm.org**

1 "Lesser Response to Angiotensin Converting Enzyme Inhibitor Therapy in Black as Compared with White Patients with Left Ventricular Dysfunction" NEJM May 3, 2001; 344: 1351-57

2 "Race and the Response to Adrenergic Blockade with Carvedilol in Patients with Chronic Heart Failure" NEJM May 3, 2001; 1358-65

Comment: The editorialist is correct in indicating that the "individual" is the authentic and final determinant by which diagnosis and therapeutic response should be measured.. However, since medicine is a statistical science, and we rely on "pretest" probabilities, I believe it is still is helpful to add race to age, sex, geographical origin, and family history to diagnostic and therapeutic decisions. An obese Pima Indian individual may not develop diabetes, and a slim "white" individual may develop diabetes, but the probabilities strongly favor the first individual.

See also "Racial Differences in Response to Drugs – Pointers to Genetic Differences" NEJM May 3, 2001; 344: 1393-96 **www.nejm.org**