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This document is divided into two parts:

1) The *Highlights* section contains brief comments patterned after the "abstract" placed on the first page of many studies reported in journals. *Highlights* condenses the content of studies, and allows a quick review of pertinent points of each article.

The *Editorial Comments* are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of *Practical Pointers*.

An *Index* containing all the Highlights is published twice a year. In an evening or two, the reader can refresh memory of the entire content of practical points abstracted from 6 major journals.

2) The main *Abstracts* section is designed as a reference. It presents structured summaries of the content of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr, M.D.
Editor/Publisher.

HIGHLIGHTS AND *EDITORIAL COMMENTS* JUNE 2005

Reduced Incidence And Severity Of HZ And PHN.

6-1 A VACCINE TO PREVENT HERPES ZOSTER AND POSTHERPETIC NEURALGIA IN OLDER ADULTS.

This study tested the hypothesis that vaccination would decrease the incidence and severity of both HZ and PHN.

Over 38 000 subjects were randomized to: 1) a subcutaneous injection of live, attenuated varicella-zoster vaccine, or 2) placebo. The potency of the live attenuated Oka vaccine was about 14 times that of the varicella vaccine given to children.

A. Herpes zoster: (3 years)	Vaccinated	Placebo	Absolute difference	NNT
Confirmed cases of acute HZ	315	642	1.7%	58
Overall incidence of HZ per 100 person-years	0.54	1.11	0.57%	175
Median duration of pain (days)	21	24		
Severity of illness	141	180 (area under the curve)		
Burden of illness score	2.2	5.7		
B. Postherpetic neuralgia (3 years)				
Confirmed cases	27	80	0.3%	333

Persistence of pain was shorter in the vaccinated group.

There was no evidence that the live vaccine caused HZ.

Adverse effects were generally mild, mainly due to local reactions.

We would expect more cases of HZ would be prevented as time progressed, and as more individuals enter the ranks of the elderly. I asked myself—at my advanced age should I take the vaccine? Having seen the devastating complications of zoster, I would be more than willing to take it, even though the likelihood of prevention of HZ over 3 years is only 1 in 58. .

Questions remain:

At what age should the vaccine be recommended?

How long is the boost in immunity protective?

Is it cost-effective enough for Medicare to cover costs?

Antibiotics Provided Little Advantage Compared With No-Antibiotics.

6-2 INFORMATION LEAFLET AND ANTIBIOTIC PRESCRIBING STRATEGIES FOR ACUTE LOWER RESPIRATORYINFECTION

Pharyngitis and acute bronchitis are the main causes of excess antibiotic prescribing.

This pragmatic study assessed the effectiveness of 3 different antibiotic strategies for acute bronchitis.

Randomized, controlled trial followed over 800 patients presenting to primary care with acute uncomplicated

LRI. Patients with findings suggestive of pneumonia were excluded—new focal chest signs (focal crepitations or bronchial breathing); and systemic features (high fever, vomiting, severe diarrhea). Also excluded patients with asthma, other chronic or acute lung diseases, cardiovascular disease, or with previous pneumonia.

Randomized to: 1) no antibiotic prescribed [control group], 2) delayed prescription [to be picked up later], or 3) immediately prescribed antibiotic. The antibiotic of choice was amoxicillin 250 mg 3 times daily for 10 days, or, if allergic, erythromycin 250 mg 4 times a day for 10 days.

Compared with no antibiotics [control group], the other strategies did not significantly alter cough duration: Delayed prescription shortened duration by 0.75 days; immediate prescription by 0.11 days. Treatment group had no effect on duration of other symptoms.

"Compared with immediate antibiotics, a strategy of either no offer of antibiotics or a delayed prescription was associated with little difference in duration or severity of symptoms." Overall, antibiotics probably do provide modest symptomatic relief. If a benefit is present, it represents a shortening of only one day in a relatively long history. "It is difficult to justify widespread antibiotic prescribing for uncomplicated lower respiratory infection on this basis, given the dangers of antibiotic resistance."

I was somewhat surprised at the duration of cough symptoms in this group of patients—a mean total of 3 weeks. However, I believe most patients would experience a gradual improvement over this period. We are admonished to consider pertussis in patient with LRI when the cough lasts 3 weeks or more. I presume in pertussis the cough continues unabated.

I believe advising patients that antibiotics may be associated with serious adverse effects (eg, colitis) will do more to tilt them toward accepting only symptomatic therapy than would advising them of the danger of antibiotic resistance in the community.

I have had success in prescribing delayed prescriptions of patients with uncomplicated lower respiratory infections. The great majority never fills the prescription. This may be an acceptable means of satisfying a demanding patient.

In the US, It is likely that many patients presenting after a week or more of cough and sputum production will receive a cheat X-ray.

The decision by primary care clinicians to prescribe or not prescribe, I believe, will often depend on how "sick" the patient appears.

A Circumference Under 100 Cm Rules Out Insulin Resistance And Hyper-Insulinemia.

6-3 USE OF WAIST CIRCUMFERENCE TO PREDICT INSULIN RESISTANCE

This study assessed how effectively different anthropometric markers used in clinical practice can predict insulin sensitivity. The authors suggest abdominal circumference is the most powerful independent predictor to rule out insulin resistance.

Determined height, weight, and waist circumference (midway between lateral lower ribs and iliac crest). Also determined results from analyses of plasma for glucose, insulin, and lipid concentrations. Used a homoeostasis index as a measure of insulin sensitivity [plasma glucose (mol/L) X plasma insulin (mU/L)/22.5]. A score of 4.0 and greater was defined as insulin resistance.

Using 100 cm as a test, the authors determined the sensitivity to diagnose insulin resistance was between 94-98%; and the specificity was between 61-63%. The positive predictive values of the test were 61% for men and 42% for women. The negative predictive value of the test was 98% in men and 97% in women. A waist circumference under 100 cm was therefore a strong independent predictor in *ruling out* insulin resistance.

Waist circumference is a simple tool to *exclude* insulin resistance. If the patient has a circumference under 100 cm (40 inches), he or she is very *unlikely* to have insulin resistance and hyper-insulinemia. Circumferences above 100 cm may, or may not, be related to insulin resistance.

I found this short article provocative. The results require confirmation. Abdominal girth is an important risk factor for the metabolic syndrome and cardiovascular disease .

6-4 SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES

The authors of the preceding article calculated the sensitivity, specificity, and predictive values of the waist circumference test.—the ability of the test to detect insulin resistance and insulin sensitivity among healthy subjects by using 100 cm as a cut-off point. I welcome opportunities to review these important statistical measures. I have done so many times. I still have some difficulty in thinking them through and calculating them accurately. I used the determinations in the article as an example.

See the abstract.

"No Indication Of A Net Benefit."

6-5 EPIDEMIOLOGICAL MODELLING OF ROUTINE USE OF LOW-DOSE ASPIRIN FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND STROKE IN THOSE AGE > 70

Current US guidelines recommend the use of low-dose aspirin for people with a 5-year absolute risk of coronary heart disease **(CH D)** of > 3%, or a 10-year absolute risk of > 10%.

"Prophylactic use of a potentially toxic agent can be problematic, particularly in people in whom comorbidity and polypharmacy are common." In a prospective observational study in two large UK general hospitals, aspirin use was the causal agent in 18% of all admissions for adverse drug effects, and was implicated in 61% of all associated deaths. Older females are the most vulnerable.

This epidemiological modeling study was conducted in a hypothetical population (10 000 men and 10 000 women) selected from a reference population from a state in Australia. All were age 70-74. None had known cardiovascular disease.

Proportional benefit gained from aspirin in prevention of MI and ischemic stroke *vs* excess hemorrhage from age 70-74 to age 100 or to death:

Benefit in preventing	Men (n = 10 000)	Women (n = 10 000)
Myocardial infarction	- 389	- 321
Ischemic stroke	- 19	- 35
Harm		
Excess GI hemorrhage	+ 499	+ 572
Excess hemorrhagic stroke	+ 76	+ 54

When comparing net harms *vs* net benefits of aspirin, the effects on length and quality of life were equivocal.

"Despite sound evidence for efficacy, the temptation to blindly implement low-dose aspirin treatment for the *primary* prevention of cardiovascular disease in elderly people must be resisted." Benefits may be offset by harms.

I believe low-dose aspirin has an important place in primary prevention of women at higher risk, and in secondary prevention of cardiovascular disease.

There is an important clinical downside related to universal prophylactic aspirin therapy: suppose primary care clinicians prescribe low-dose aspirin to 1000 women over 10 years. Three or 4 ischemic strokes might be prevented. But there would be no way of knowing which individuals of the 1000 benefited. Conversely, a serious hemorrhagic event occurring in 2 of the1000 patients would be self-evident. The clinician might feel responsible, and the patient and family might blame the clinician for the disaster.

I believe primary prevention with aspirin in women at average risk should be avoided. Obviously, careful clinical judgment based on individual-patient attributes is required.

"Our Most Important Finding Was The High Level Of Antipsychotic Prescribing In NHs."

6-6 THE QUALITY OF ANTIPSYCHOTIC DRUG PRESCRIBING IN NURSING HOMES

Antipsychotic drug prescribing in nursing homes **(NHs)** has been rising.

Federal statutes are in effect to protect NH residents from receiving inappropriate antipsychotics. They may be appropriately prescribed for delirium and dementia only if psychotic features or dangerous behaviors are present. Guidelines also stipulate maximum daily doses.

For residents with dementia, behavioral assessments must also show evidence of verbal or physical aggression or delusions or hallucinations.

Impaired memory, wandering, restlessness, unsociability, uncooperativeness, and indifference to surroundings are NOT indications.

Use of antipsychotic drugs in NHs was widespread. Most atypicals were prescribed outside the prescribing guidelines with doses, and for indications without strong clinical evidence of benefit. About 1 in 4 received doses exceeding recommended. About 2/3 of use was appropriate—dementia with aggressive behavior; dementia with delusions; psychotic disorder. About 1/3 received the drugs inappropriately—impaired memory; depression without psychotic features; indifference to surroundings; insomnia; anxiety; wandering; restlessness; uncooperativeness; unsociability.

The study failed to detect positive relationships between behavioral symptoms and antipsychotic therapy.

"This study raises questions about the current uses of antipsychotics in NHs."

These are powerful drugs. Elderly patients are subject to more adverse effects. They require a lower dose because of impaired renal function and concomitant illness. The PDR reiterates that schizophrenia is the only indication. There is no mention of use in nursing homes. Few studies have concerned patients over age 65.

I believe the most appropriate question to ask when contemplating use of antipsychotics in NHs is . . . Am I prescribing this drug to benefit the patient, or the nursing staff and the family? This can be a most difficult decision to make. If they are prescribed, individual- patient's response must be carefully monitored.

When To Intervene? How To Intervene?

6-7 Thresholds For Normal Blood Pressure And Serum Cholesterol.

In 2003, European guidelines suggested a BP of above 140/90, and a cholesterol above 5 mmol/L (193 mg/dL) as the appropriate thresholds for intervention. "The bottom line is that the doctor is expected to inform the patient that these measurements mean that he or she is at increased cardiovascular risk regardless of the management proposed. In other words, a disease label is to be attached to the patient."

In Norway, if this threshold for cholesterol and BP were to be applied at age 24, half the population would be identified as being at increased risk. At age 49, the proportion is raised to 90%. As much as 75% of the total population would be identified as being at risk.

The potential benefits for treated patients become less at lower risk levels. The number needed to treat is increased. The rates of adverse effects (of drug treatment) remain the same. Adverse effects tend to be under-reported and under-published.

Certainly, experts who developed these guidelines did not suggest that all persons with BP and cholesterol levels above these cut-points should be treated with drugs.

I believe however, that all should be treated with judicious advice about changing in lifestyle. This will apply to almost all persons in the US over age 50. Very rarely will individuals over age 50 have no risk factors. Cut-points are defined at levels below which no further reduction in risk occurs. Admittedly, those with baseline risk-levels at the low range will have less to gain when their levels are lowered than persons with high baseline risk-levels.

I do not believe life-style advice will be interpreted as a labeling of disease. There are few if any adverse effects of lifestyle changes. Effectiveness is established. The benefit/harm-cost ratio is very low.

The task of educating patients about healthy lifestyles and getting them to adopt them is daunting, and in the main unsuccessful. We should not be deterred from trying. This includes primary care clinicians' adopting a healthy lifestyle themselves.

Who should be treated with drugs?—patients who are indeed at high risk. The definition of "high risk" depends not only on the number or risk factors present and their levels, but also on the individual patient's assessment of his own risk. Patients must be convinced of the benefits of drug therapy; must understand that drug therapy is long-term, expensive, and carries risks of its own.

No Evidence Of Superiority For Treatment With A Calcium Channel-Blocker, Or An ACE Inhibitor Compared With A Thiazide-Type Diuretic

6-8 CLINICAL OUTCOMES IN ANTIHYPERTENSIVE TREATMENT OF TYPE 2 DIABETES, IMPAIRED FASTING GLUCOSE CONCENTRATION, AND NORMOGLYCEMIA

The Antihypertensive and Lipid-lowering Treatment to prevent Heart Attack Trial (ALLHAT)

This is one of a series of articles reported by the ALLHAT group.

There was no evidence of superiority for treatment with a calcium channel-blocker, or an ACE inhibitor compared with a thiazide-type diuretic during first-step antihypertension therapy in DM, IFG, or NG.

Most hypertensive patients with DM or IFG or impaired glucose tolerance, I believe, would receive more than one antihypertension drug. Many clinicians would use a combination of an ACE inhibitor and a diuretic.. Any combination should include a thiazide.

The abstract of this study is brief since I already abstracted similar studies by the same ALLHAT group:

A. JAMA December 18, 2002; 2981-97 presented the original ALLHAT study. (See Practical Pointers December 2002 [12-1]) The study compared the same 3 drugs in similar patients with hypertension and at least one additional risk factor (high-risk) . Conclusion: "Thiazide-type diuretics should be considered first for pharmacological therapy in patients with hypertension. " They are unsurpassed in lowering BP, reducing clinical events, and in tolerability. They are much less costly. Since many patients with hypertension will require more than one drug to control their BP, it is reasonable to infer that a diuretic should be included in all multidrug regimens.

B. JAMA April 6, 2005; 293: 1595-1608 (See Practical Pointers April 2005 [4-2]) "Thiazide-type diuretics remain the drugs of first choice for initial therapy of hypertension in both black and non-black hypertensive patients."

C. Archives Int Med April 25, 2005; 165: 936-46. "Renal Outcomes in High-Risk Hypertensive Patients with an Angiotensin-Converting Enzyme Inhibitor or a Calcium Channel Blocker vs Diuretic." In hypertensive patients with reduced glomerular filtration rate, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing the rate of development of end-stage renal disease or a 50% or greater reduction of glomerular filtration rate.

See also:

NEJM December 30, 2004; 351: 2805-16 (Practical Pointers December 2004 [12-2]) "Association between Cardiovascular Outcomes and Antihypertensive Treatment in Older Women" Conclusion: Monotherapy with diuretics was equally or more effective than other monotherapies. The combination of diuretics + beta-blockers was superior to, or equally effective as, other combinations.

Likely To Produce Clinically Important Pain Relief.

6-9 EFFICACY AND SAFETY OF OPIOID AGONISTS IN THE TREATMENT OF NEUROPATHIC PAIN OF NON-MALIGNANT ORIGIN A Systematic Review.

Effective pain relief in these patients is difficult to achieve. Use of opioids is controversial. This is in part because studies have been small, have yielded equivocal results, and have not established long-term efficacy and safety. There have been concerns about adverse effects: potential for abuse and addiction, hormonal abnormalities, dysfunction of the immune system, and paradoxical hyperalgesia.

This systematic review assessed the efficacy and safety of opioids for treatment of NP.

Opioid treatment for 1 to 8 weeks had a beneficial effect over placebo for spontaneous neuropathic pain. The magnitude of this opioid effect was nearly a 14-point difference in pain intensity at study end compared with placebo. Is an average decline of 14 points on a 100-point scale meaningful to patients? The mean initial pain intensity ranged from 46 to 69. A 14-point difference corresponds to a 20% to 30% reduction in pain.

The trial did not address issues of addiction. It is reasonable to assume that the studies did not include individuals who might be potential abusers.

The most common adverse effects were nausea, constipation, drowsiness, vomiting, and dizziness. (NNT to harm one patient = 4 to 7.)

I believe primary care clinicians underuse opioids for patients with non-cancer pain. Fears of addiction have been overemphasized.

Donepezil May Delay Clinical Progression To Alzheimer's Disease

6-10 VITAMIN E AND DONEPEZIL (*ARICEPT*) FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT

Amnestic (memory loss) mild cognitive impairment **(MCI)** represents a transitional state between the cognitive changes of normal aging and the earliest clinical features of Alzheimer's disease **(AD).** Amnestic MCI refers to the subtype that has a primary memory component, either alone or in conjunction with other cognitive-domain impairments, of insufficient severity to constitute dementia. About 80% of those who meet the criteria for MCI will have AD within 6 years.

MCI is a transition state between normal aging and dementia (for Alzheimer's disease in particular), one in which cognitive deficits are present, but function preserved. In clinical settings, the term is often used to describe patients who present with memory loss, but do not have dementia. Even when defined carefully, MCI is a heterogeneous category that includes some persons with memory changes of normal aging, some with non-progressive cognitive defects, some with prodromal AD, and some with prodromal forms of other neurodegenerative dementias.

This study was designed to determine if vitamin E or the cholinesterase inhibitor donepezil could delay the clinical diagnosis of AD in patients with MCI.

Vitamin E had no effect at any time.

For donepezil . . . "The observed relative reduction in the risk of progression of 56% at one year and 36% at two years in the entire cohort is likely to be clinically significant."

"Although our findings do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment, they could prompt a discussion between the clinician and the patient about this possibility."

Symptoms of memory loss in older persons should be taken seriously. They may represent the beginning of AD. This may be an important clinical measure once more effective treatments become available.

The important question is . . . What are the cognitive changes of normal aging?

I believe some degree of memory impairment is almost universal among individuals over age 80. It usually begins by forgetting names, and recalling them minutes or hours later ("senior moments"). The spectrum of memory impairment is wide. The definition of amnestic MCI is not settled. At what point does it predict development of AD? The criteria for diagnosis of amnestic MCI in the study included patients with difficulties greater than temporarily forgetting names.

This study may foretell important developments in drug therapy which may delay the onset of disabling dementia. The spectrum of forgetfulness of old age is very broad. When should intervention be considered? Some elderly patients may well accept early intervention. A delay of one to two years represents a large proportion of remaining quality-life. Patients may be willing to accept some adverse effects of drugs to gain a few years free of dementia of AD. (Note that anticholinergics do not benefit vascular dementia.)

Others may wish to wait until adverse effects on daily living become more evident.

I do not believe memory defects inevitably progress to AD. Keeping mentally and physically active, continuing a healthy diet, retaining active family and social connections, and controlling risk factors for cardiovascular disease will delay or prevent development of dementia in many individuals.

In Modestly Overweight Persons, Reduction In Weight May Lower Risk Of Developing Hypertension.

6-11 WEIGHT LOSS IN OVERWEIGHT ADULTS AND THE LONG-TERM RISK OF HYPERTENSION: The Framingham Study

Obesity is associated with higher levels of insulin resistance, hyperinsulinemia, rises in cardiac output, increases in cholesterol and triglycerides, and increased sympathetic nervous system activity. Most of these changes have been associated with increases in BP. "In recent years, there has been a great deal of focus on the roles of hyperinsulinemia and insulin resistance in the development of hypertension."

The goal of this study was to estimate the effects of both the amount on weight loss and the persistence of weight loss on the risk of incident hypertension among already obese adults. (*Primary prevention.)*

After multiple adjustments, weight loss of 6.8 kg (18 pounds) or more led to a 28% reduction in risk of developing long-term hypertension in younger subjects (mean age 27) , and a 37% reduction in older subjects (mean age 52).

If the weight loss was sustained over the years, the risks of developing hypertension were reduced by 22% and 26%.

"The results of this study suggest that at least 15% of the cases of hypertension in overweight middle-aged adults and 22% of the cases occurring in overweight older adults could be prevented by a modest amount of sustained weight loss."

Overweight + hyperinsulinism + dyslipidemia + hypertension = a common and deadly combination

Treatment Reduced Serious Perinatal Morbidity In Infants And May Improve The Woman's Health-Related Quality Of Life.

6-12 GESTATIONAL DIABETES MELLITUS; Effect Of Treatment On Pregnancy Outcomes.

Gestational diabetes mellitus **(GDM)** occurs in up to 9% of all pregnancies. It is associated with substantial maternal and perinatal complications. Neonatal complications include macrosomia, shoulder dystocia, birth injuries, bone fractures, nerve palsies, and hypoglycemia. Long-term adverse health outcomes among infants born to mothers with GDM include sustained glucose intolerance, subsequent obesity, and impaired intellectual achievement.

This study asked . . . Does screening and treatment for GDM reduce these risks?

This randomized trial enrolled 1000 women who were between 16 and 30 weeks pregnant. Randomized to: 1) An intervention group received expert diabetes care including education, self-monitoring blood glucose, and adjusted insulin therapy, and 2) A usual care group.

Serious perinatal complications in infants were significantly lower in the intervention group (1% vs 4%). The NNT to prevent one serious outcome in infants = 34. Birth weights were lower in the intervention group (less likely to have macrosomia). No difference in rate of hypoglycemia requiring intravenous glucose.

Women in the intervention group gained less weight and had less risk for preeclampsia. At 3-months postpartum, women had lower rates of depression and higher scores on quality-of-life. Rates of caesarean deliveries were similar.

Impaired glucose tolerance and diabetes are important risk factors at the time of conception. Primary care clinicians can serve their young adult female patients by advising them of the risks of glucose intolerance (and excessive weight) before and at the time of conception.

The Test Could Be Used As An Initial Approach To Diagnosis.

6-13 IS PROTON PUMP INHIBITOR TESTING AN EFFECTIVE APPROACH TO DIAGNOSE GASTRO ESOPHAGEAL REFLUX DISEASE IN PATIENTS WITH NON-CARDIAC PAIN? A Meta-analysis

Gastro esophageal reflux disease **(GERD)** is the most common cause of non-cardiac chest pain **(NCCP).** Patients with NCCP are often treated empirically and successfully with proton pump inhibitors.

This study asked. . .Can proton pump inhibitors (a PPI test) be used as a *diagnostic* test?

Results of the PPI test:

	GERD present	GERD absent
Positive test (> 50% relief)	80% (true positive)*	26% (false positive)
Negative test (< 50% relief)	20% (false negative)	74% (true negative test)**

(* sensitivity of the PPI test = true + % = 80%; ** specificity of the PPI test = true negative % = 74%)

Results of the placebo test:

Positive test (> 50% relief)	19% (true positive)***	23% (false positive)
Negative test (< 50% relief)	81% (false negative)	77% (true negative test)****

(*** sensitivity of placebo test =19%; **** specificity of placebo test = 77%)

Thus 80% responded favorably to PPI *vs* 19% to placebo.

Treatment with PPIs and placebo showed similar effects (26% and 23%) on improving NCCP symptoms in patients *without* GERD, indicating a possible placebo effect.

The use of PPI as a diagnostic test for detecting GERD in patients with NCCP has an "acceptable" sensitivity and specificity and could be used as an initial approach by primary care physicians to detect GERD in selected patients with NCCP.

"Acceptability of the test would be more meaningfully determined by calculating pre-test probability., likelihood ratios, and post-test probability. See the full abstract.

Regardless of the modest diagnostic help given by a PPI test, I believe, in practice, the test is used extensively by primary care clinicians and their patients.

May Reduce Risk Of Development Of PMS.

6-14 CALCIUM AND VITAMIN D INTAKE AND RISK OF INCIDENT PREMENSTRUAL SYNDROME

Several studies have suggested that calcium and vitamin D levels are lower in women with PMS, and that calcium supplementation may prevent the initial development of PMS.

This case-control study was nested within the large prospective Nurses' Health Study. Participants were a subset of women age 27 to 44 (mean = 35). All were free of PMS at baseline (1991). Cases: 1057 women who developed PMS over a 10-year follow-up. Controls: 1968 women who reported no diagnosis of PMS and no, or minimal, menstrual symptoms.

Determined dietary and supplemental intakes of calcium and vitamin D by periodic questionnaires.

Women in the highest quintile of total vitamin D intake (median of 706 IU) had a relative risk of new-onset PMS of 0.59 compared with those in the lowest quintile (median of 112 IU). Benefit was associated with vitamin D from food. Supplemental vitamin D did not seem to be associated with risk.

Similar benefit was associated with calcium intake from food.

I abstracted this article because its conclusions are provocative—certainly not definitive. It raises more questions: Why did the benefit not extend to supplements? Is there a reasonable biological mechanism for the action of calcium and vitamin D? Why no benefit from whole milk? At a more practical level—could diet be beneficial in treatment as well as prevention?

I will watch for more developments.

Hope For Reducing The Prevalence Of This World-Wide Scourge.

6-15 BASIC SCIENCE GUIDELINES DESIGN OF NEW TB VACCINE CANDIDATES

Several new vaccines which improve immune response are under investigation. They may be helpful in primary prevention of infection as well as boosting immunity in those with latent infection.

See the abstract.

(*The entire June 8 2005 issue of JAMA is devoted to tuberculosis.)*

ABSTRACTS JUNE 2005

Reduced Incidence And Severity Of HZ And PHN.

6-1 A VACCINE TO PREVENT HERPES ZOSTER AND POSTHERPETIC NEURALGIA IN OLDER ADULTS.

Cell-mediated immunity declines with age. This increases likelihood of reactivation of the latent varicella-zoster virus within the sensory ganglia, causing herpes zoster **(HZ).** Complications of HZ occur in about 50% of elderly patients, most commonly postherpetic neuralgia **(PHN).**

The pain of PHN can be prolonged and disabling. It can diminish the patient's quality of life and ability to function to a degree comparable to that of diseases such as congestive heart failure, myocardial infarction, type 2 diabetes, and major depression.

Antiviral therapy reduces the severity and duration of the acute phase of HZ, but does not prevent PHN.

Recurrences of HZ are uncommon among immunocompetent persons because an episode of acute HZ boosts immunity, effectively "immunizing" against a subsequent attack.

Vaccines can elicit a significant increase in cell-mediated immunity to HZ in immunocompetent older adults.

This study tested the hypothesis that vaccination would decrease the incidence and severity of both HZ and PHN.

Conclusion: The vaccine markedly reduced incidence and severity of HZ and PHN.

STUDY

1. A randomized, double-blind placebo-controlled trial enrolled over 38 000 adults. All were over age 60 (46% over age 70).
2. Randomized to: 1) a subcutaneous injection of live, attenuated varicella-zoster vaccine, or 2) placebo.
   The potency of the live attenuated Oka vaccine was about 14 times that of the varicella vaccine given to children.
3. Determined incidence, severity and duration of subsequent acute HZ, and incidence of PHN.

RESULTS

1. Over 95% of subjects completed the 3-year study.
2. Outcome:

A. Herpes zoster: (3y)	Vaccinated	Placebo	Absolute difference	NNT
Confirmed cases of acute HZ	315	642	1.7%	58
Overall incidence of HZ				
per 100 person-years	0.54	1.11	0.57%	175
Median duration of pain (d)	21	24		
Severity of illness	141	180 (area under the curve)		
Burden of illness score	2.2	5.7		

B. Postherpetic neuralgia (3y)

Confirmed cases	27	80	0.3%	333

Persistence of pain was shorter in the vaccinated group.

3. During the first 42 days after vaccination, 7 cases of HZ occurred in the vaccine group vs 24 in the placebo group. (Apparently the boost in immunity occurs quickly.)
4. The results of PCR testing were positive for wild-type varicella-zoster virus DNA in over 93% of cases. The vaccine virus DNA was not detected in any case. (Ie, the live vaccine does not cause HZ.)
6. Adverse events:

Serious adverse events—number and types of were similar in both groups.

Local reactions (especially erythema and tenderness) were more common in the vaccine group. They were usually mild.

Hospitalizations were similar and not considered related to the vaccine. No vaccine recipient developed fever over 38.3^0

DISCUSSION

1. An estimated 1 million cases of HZ occur in the US each year. The number is expected to increase as the population ages.
2. In older subjects in the study, the benefit of the vaccine in reducing incidence of HZ was less, but the effect on reducing severity of the illness was greater.
3. The potency of the vaccine was much greater than the vaccine given to children. “We do not recommend the use of the current varicella vaccine in an attempt to protect against herpes zoster and postherpetic neuralgia.”

CONCLUSION

The vaccine markedly reduced morbidity from acute HZ, and PHN.

NEJM June 2, 2005; 352: 2271-84 Original investigation by the Shingles Prevention Study Group, first author M N Oxman, VA San Diego Health-care System, CA.

An editorial in this issue of NEJM (pp 2344-46) by Donald H Gilden, comments:

Should vaccine be recommended for all VZV-seropositive middle-aged adults who have not had zoster? The author suggests that grown-ups should welcome the vaccine. “We may need it more than children do.” He cites 2 considerations:

1) What is the future risk of zoster among adults who were vaccinated for chickenpox in childhood? At present, most elderly people have not been vaccinated. By 2047, most middle-aged Americans will have received chickenpox vaccine. They have not had chickenpox. Like the wild-type virus, the live Oka varicella vaccine virus given to children becomes latent in ganglia. If the viral burden is less in adults who were vaccinated in infancy—compared with adults who have had chickenpox in childhood—then the incidence of zoster may be reduced. Would the vaccine be indicated in this group?

2) Cost-effectiveness: This depends on price. It may be that the adult vaccine, given its greater potency, will be more expensive than the childhood vaccine. Nevertheless, the zoster vaccine appears to be highly cost-effective even assuming a cost of $500.

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"No Difference in Symptom Relief"

6-2 INFORMATION LEAFLET AND ANTIBIOTIC PRESCRIBING STRATEGIES FOR ACUTE LOWER RESPIRATORYINFECTION

Pharyngitis and acute bronchitis are the main causes of excess antibiotic prescribing. Costs each year exceed $700 million. A consensus has been made for limiting use of antibiotics in lower respiratory infections. **(LRI).** But recent systematic reviews have come to diverse conclusions about the effectiveness of antibiotics. The most recent Cochrane review confirms a moderate benefit of antibiotics on the course of the illness, but called for more evidence. Reviews have concerned relatively small numbers of patients.

Strategies to treat *upper* respiratory which do not include initial antibiotics—either no antibiotics or delayed antibiotics—are effective in up to 90% of cases, result in acceptable symptom control, are satisfactory to the patient, and can reduce reconsultation by up to 40%.

The debate about use of antibiotics for lower respiratory infections continues.

This pragmatic study assessed the effectiveness of 3 different antibiotic strategies, and the effectiveness of an information leaflet given to patients compared with brief verbal information alone.

Conclusion: There was no difference in symptom resolution between immediate prescription of antibiotic, no prescription for antibiotic, and delayed prescription. The information leaflet was of little help.

STUDY

1. Randomized, controlled trial followed over 800 patients presenting to primary care with acute uncomplicated LRI. Patients with findings suggestive of pneumonia were excluded—new focal chest signs (focal crepitations or bronchial breathing); and systemic features (high fever, vomiting, severe diarrhea). Also excluded patients with asthma, other chronic or acute lung diseases, cardiovascular disease, or with previous pneumonia.
2. The patients included 17% under age 16 and 17% over age 60. (mean age 39). They were moderately ill. The majority had fever, sore throat, and coryza. Many were producing dark green sputum. Some had coarse crepetitations and wheeze.
3. The mean duration of cough before the first consultation was 9 days.
4. Randomized to: 1) no antibiotic prescribed [control group], 2) delayed prescription [to be picked up later], or 3) immediately prescribed antibiotic. The antibiotic of choice was amoxicillin 250 mg 3 times daily for 10 days, or, if allergic, erythromycin 250 mg 4 times a day for 10 days.
5. The delayed prescription was left in a box in the reception room of the office to be picked up at any time the patients wished.
6. Patients were also randomized to receive, or not receive, an information leaflet describing the natural

history of acute LRI. (*I omit this data, since it provided little benefit compared with a brief oral consultation. RTJ*)

7. Patients were asked to record their temperatures. They also were asked to keep a diary and record use of antipyretics, and severity of 6 symptoms—cough, dyspnea, sputum production, well-being, sleep disturbance, and activity disturbance.

RESULTS

1. After the consultation, cough rated as at least a "slight problem" lasted for a mean of 12 days (25% over 17 days).
2. Compared with no antibiotics [control group], the other strategies did not significantly alter cough duration: delayed prescription shortened duration by 0.75 days; immediate prescription by 0.11 days. Treatment group had no effect on duration of other symptoms.
3.

	Immediate	Delayed	Control (none prescribed)
Use of antibiotics:	96%;	20%;	16%.
Patients "very satisfied"	86%;	77%,	72%.
Believed antibiotics to be effective	75%	40%	47%
Re-attendance within 1 month	11%	12%	19%

(*Note that relatively few of the delayed group actually had prescriptions filled.)*

4. Adverse events; one patient (of 212) in the no antibiotic group developed pneumonia. He was hospitalized and treated with antibiotics. He recovered fully.

DISCUSION

1. There is no widely agreed definition of lower respiratory infection. In practice, most patients have cough with sputum.
2. "Our study confirms the long history of lower respiratory infection. Patients need to be warned that they will on average have an illness lasting 3 weeks in total with10 days of symptoms before the physician visit and 12 days after the physician visit."
3. "Compared with immediate antibiotics, a strategy of either no offer of antibiotics or a delayed prescription was associated with little difference in duration or severity of symptoms." Overall, antibiotics probably do provide modest symptomatic relief. If a benefit is present, it represents a shortening of only one day in a relatively long history. "It is difficult to justify widespread antibiotic prescribing for uncomplicated lower respiratory infection on this basis, given the dangers of antibiotic resistance."
4. A high percentage of patients receiving no antibiotics or delayed prescription for antibiotics were satisfied with their treatment.
5. The practice of no offer of antibiotics and delayed prescription for antibiotics is likely to reduce use of antibiotics.

CONCLUSION

For patients with LRI, not prescribing antibiotics or offering a delayed prescription (compared with immediate prescription) was associated with little difference in symptom resolution.

JAMA June 22/29, 2005; 293: 3029-35 Original investigation, first author Paul Little, University of Southampton, UK.

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A Circumference Under 100 Cm Rules Out Insulin Resistance And Hyper-Insulinemia.

6-3 USE OF WAIST CIRCUMFERENCE TO PREDICT INSULIN RESISTANCE

Insulin resistance is an important component of the metabolic syndrome. No easy clinical test exists to determine insulin resistance in an individual.

This study assessed how effectively different anthropometric markers used in clinical practice can predict insulin sensitivity. The investigators analyzed a sample of 2746 healthy volunteers (798 male) from retrospectively collected data. Ages ranged from 18 to 72; body mass indexes from 18 to 60; and waist circumferences from 65 cm to 150 cm.

Determined height, weight, and waist circumference (midway between lateral lower ribs and iliac crest). Also determined results from analyses of plasma for glucose, insulin, and lipid concentrations. Used a homoeostasis index as a measure of insulin sensitivity [plasma glucose (mol/L) X plasma insulin (mU/L)/22.5]. A score of 4.0 and greater was defined as insulin resistance.

Assessed predictive power of 5 variables: waist circumference; plasma triglycerides; systolic BP; HDL-cholesterol; and body mass index.

Set the optimal abdominal circumference cut-point for detecting insulin resistance at 100 cm (40 inches) for both men and women. Using 100 cm as a test, the authors determined the sensitivity to diagnose insulin resistance was between 94-98%; and the specificity was between 61-63%. The positive predictive values of the test were 61% for men and 42% for women. The negative predictive value of the test was 98% in men and 97% in women. A waist circumference under 100 cm was therefore very predictive in *ruling out* insulin resistance. (These figures depend on the prevalence of insulin resistance in the actual sample.)

COMMENT

1. Some studies report that the prevalence of the metabolic syndrome is similar in both sexes.
2. “A waist circumference under 100 excluded individuals of both sexes from the risk of being insulin resistant.”
3. At a cut point of 88 cm (currently recommended for women) the specificity drops markedly. (Too many false positives for insulin resistance.) “Abdominal obesity is overestimated in women.”

CONCLUSION

Waist circumference is a simple tool to *exclude* insulin resistance. If the patient has a circumference under 100 cm, he or she is very unlikely to have insulin resistance and hyper-insulinemia. Circumferences above 100 cm (40 inches) may, or may not, be related to insulin resistance.

BMJ June 11, 2005: 330: 1363-64 Original investigation, first author Hans Wahrenberg, Karolinska Institute, Stockholm, Sweden.

6-4 SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES: A Review By The Editor

The authors of the preceding article calculated the sensitivity, specificity, and predictive values of the waist circumference test.—the ability of the test to detect insulin resistance and insulin sensitivity among healthy subjects by using 100 cm as a cut-off point. I welcome opportunities to review these important statistical measures. I have done so many times. I still have some difficulty in thinking them through and calculating them accurately. I used the determinations in the article as an example.

SENSITIVITY

Start by considering *only* subjects who have the disease, in this case insulin resistance.

Sensitivity of the 100 cm test for men:

Sensitivity of the test = % of subjects who have the disease (insulin resistance) who have a positive test (waist 100 cm and above)—ie, the true positive %.

	Insulin resistance present (n = 284)
(The test)	(disease present)
Waist 100 cm and above (true positive test)	277
Waist under 100 cm (negative test)	7
Total	284

The sensitivity of the test for men = 277/284 = 98% (the true positive %)

By the same calculations the sensitivity of the test in women = 63%.

SPECIFICITY

Start by considering *only* subjects who do *not* have the disease—are not insulin resistant (are insulin sensitive)

Specificity of the 100 cm test for men:

Specificity of the test = % of subjects who do not have the disease (are insulin sensitive) who have a negative test (waist under 100 cm—the true negative %).

	Insulin sensitive (n = 469)
(The test)	(disease absent)
Waist 100 cm and above (false positive test)	176
Waist under 100 cm (true negative test)	293
Total	469

Specificity of the test for men =true negative % = 293/469 = 63%

By the same calculations the specificity of the test in women = 97%

PREDICTIVE VALUE OF POSITIVE TESTS (POSITIVE PREDICTIVE VALUE)

Start by considering only subjects in the cohort who have a positive test.

Among men who have positive tests (both true positive and false positive) what percentage are true positives?

In this cohort of men:	Positive tests	
True positive tests	277	The predictive value of a positive test = true positive/total
False positive tests	176	positive = 277/453 = 61%. (Not discriminating)
Total tests	453	

PREDICTIVE VALUE OF NEGATIVE TESTS (NEGATIVE PREDICTIVE VALUE)

Start by considering only subjects in the cohort who have a negative test.

In this cadre of men	Negative tests	
True negative tests	293	The predictive value of a negative test = true negative/total
False negative tests	7	negative = 293/300 = 98%
Total tests	300	(Very discriminating)

For a man with a waist circumference below 100 cm, the likelihood that he had insulin resistance was very low. (98%)

For women, negative predictive value was 97%. If a woman had a waist circumference less than 100 cm, the likelihood that she had insulin resistance was also very low.

Practical Pointers for Primary Care June 2005 Comments by the editor

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"No Indication Of A Net Benefit."

6-5 EPIDEMIOLOGICAL MODELLING OF ROUTINE USE OF LOW-DOSE ASPIRIN FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND STROKE IN THOSE AGE > 70

Current US guidelines recommend the use of low-dose aspirin for people with a 5-year absolute risk of coronary heart disease **(CH D)** of > 3%, or a 10-year absolute risk of > 10%. In Australia, about 2/3 of all people age 70-74 (94% of men and 46% of women) have an estimated 10-year absolute risk of 10% or over.

"Prophylactic use of a potentially toxic agent can be problematic, particularly in people in whom comorbidity and polypharmacy are common." In a prospective observational study in two large UK general hospitals, aspirin use was the causal agent in 18% of all admissions for adverse drug effects, and was implicated in 61% of all associated deaths. Older females are the most vulnerable.

Most primary prevention trials are conducted in middle-aged people, not in the elderly.

This study investigated the benefit of routine use of low-dose aspirin in people over age 70 who had no history of overt cardiovascular disease.

Conclusion; Any benefits are likely offset by adverse effects.

STUDY

1. This epidemiological modeling study was conducted in a hypothetical population (10 000 men and 10 000 women) selected from a reference population from a state in Australia. All were age 70-74. None had known cardiovascular disease.
2. Main outcome measure = first ever myocardial infarction **(MI),** stroke, or gastrointestinal hemorrhage.
3. Calculated health-adjusted years of life lived related to use of low-dose aspirin from age 70-74 until death or age 100.

RESULTS

1. Proportional benefit gained from aspirin in prevention of MI and ischemic stroke *vs* excess hemorrhage:

Benefit in preventing	Men (n = 10 000)	Women (n = 10 000)
Myocardial infarction	- 389	- 321
Ischemic stroke	- 19	- 35
Harm		
Excess GI hemorrhage	+ 499	+ 572
Excess hemorrhagic stroke	+ 76	+ 54

2. When comparing net harms vs net benefits of aspirin, the effects on length and quality of life were equivocal.

DISCUSSION

1. The model suggests that benefit gained from routinely prescribing low-dose aspirin to patients aged 70 and above in terms of preventing first ever cardiovascular events would be offset by a greater occurrence of gastrointestinal and intracerebral bleeding. “On balance, there was no indication of a net benefit.” However, because of the uncertainty in the assumptions, the balance of harm and benefit could tip in either way.
2. Consideration needs to be given to possible adverse effects, especially in special risk groups such as elderly people.
3. Due to the wide confidence intervals determined by the study, the overall outcome could be beneficial or adverse.

CONCLUSION

“Despite sound evidence for efficacy, the temptation to blindly implement low-dose aspirin treatment for the *primary* prevention of cardiovascular disease in elderly people must be resisted.” Benefits may be offset by harms.

BMJ June 4, 2005; 330: 1306-08 “Primary Care”, original investigation, first author Mark R Nelson, University of Tasmania, Hobart.

An editorial in Annals Int Med June 7, 2005, first author Cynthia Mulrow, Deputy Editor, comments on the recently published study (*NEJM 2005; 352: 1293-304)* of aspirin in primary prevention in a large group of healthy women over age 45 who were at average risk:

Effect of low-dose aspirin over 10 years:

All-cause mortality: little or no effect

Ischemic strokes prevented: 3 to 4

Myocardial infarction: little or no effect

Hemorrhagic strokes caused: 0 to 1

Major gastrointestinal bleeding: 1

There was some evidence that women over age 65 benefited more, but they also are at risk for more serious adverse effects.)

Reviewing a landmark study 16 years on:

FINAL REPORT ON THE ASPIRIN COMPONENT OF THE ONGOING PHYSICIANS' HEALTH STUDY ***NEJM July 20, 1989;321: 130***

This landmark primary prevention study led to use of low-dose aspirin by millions of men in the US, including many primary care clinicians.

Over 22 000 male physicians entered a double-blind, placebo-controlled 5-year trial: 1) 325 mg aspirin every other day vs 2) placebo. The benefit of aspirin was significant—a 44% reduction in risk of myocardial infarction (MI). Benefit was evident only for men over age 50.

In absolute terms, over 100 000 person-years of aspirin use, 183 myocardial infarcts were prevented (~ 2/1000 per year). When non-fatal MI, non-fatal stroke, and cardiovascular deaths were combined, the reduction in risk in the aspirin group was lowered to 18%. (NNT for one year to prevent one event = 2000)

Total stroke and hemorrhagic stroke were non-significantly increased in the aspirin group. Cardiovascular mortality was unchanged. There was a trend toward greater benefit in individuals with risk factors—elevated cholesterol, family history of CVD, diabetes, smokers, and history of hypertension.

The trial did not include females and the very elderly.

I believe many primary care physicians extrapolated the results and prescribed prophylactic aspirin to women.

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Indicated Only If Psychotic Features Or Dangerous Behaviors Are Present.

6-6 THE QUALITY OF ANTIPSYCHOTIC DRUG PRESCRIBING IN NURSING HOMES

Antipsychotic drug prescribing in nursing homes **(NHs)** has been rising. This is attributed to the availability of second-generation agents.[1] These "atypical" agents have replaced the older conventional agents, and have

transformed therapeutic applications. In practice, use has been expanded to indications outside those approved by the FDA. The influence of atypicals in NHs is especially remarkable because antipsychotic drug use must adhere to prescribing guidelines of appropriateness. This limits off-label use.

There are concerns about the quality of care, especially when discordant with prescribing guidelines. Most atypicals have been approved because of demonstrated efficacy for schizophrenia. Yet, they are increasingly being prescribed for other reasons, based on less evidence. In 1986, the Institute of Medicine reported widespread misuse to sedate or discipline NH residents.

In NHs, atypicals are prescribed mainly for behavioral and psychological symptoms associated with dementia, even though the clinical findings of benefit are equivocal. Safety is also under review. Serious adverse events have been associated with use—falls, somnolence, and abnormal gait. (*And even deaths.)*

Federal statutes are in effect to protect NH residents from receiving inappropriate antipsychotics. They may be appropriately prescribed for delirium and dementia only if psychotic features or dangerous behaviors are present. Guidelines also stipulate maximum daily doses.

For residents with dementia, behavioral assessments must also show evidence of verbal or physical aggression or delusions or hallucinations.

Impaired memory, wandering, restlessness, unsociability, uncooperativeness, and indifference to surroundings are NOT indications.

This study assessed prevalence of antipsychotic use in nursing homes, rates of adherence to prescribing guidelines, and resultant changes in behavior in recipients.

Conclusion: Use of anti-psychotic drugs in NHs was widespread. Most atypicals were prescribed outside the prescribing guidelines, with doses, and for indications without strong clinical evidence of benefit. The study failed to detect positive relationships between behavioral symptoms and antipsychotic therapy.

STUDY

1. Retrospective analysis using nationally representative data from Medicare assessed prevalence of use of anti-psychotics, rates of adherence to guidelines, and resultant changes in behavioral symptoms.

RESULTS

1. An estimated 45% of Medicare beneficiaries in NHs had indications appropriate for antipsychotic therapy. (*This far exceeds my experience. RTJ*) Behavioral problems, especially physical and verbal aggression, were more common among recipients relative to non-users.
2. An estimated 28% of residents of NHs received at least one antipsychotic during the study period. This approximates over 650 000 patients; 20% of residents received atypicals. Spending for antipsychotics has increased substantially.
3. Many residents received therapy outside the prescribing guidelines. One in 4 had no appropriate indication. About 1 in 4 received doses exceeding recommended.
4. About 2/3 of use was appropriate: dementia with aggressive behavior; dementia with delusions; psychotic disorder.

5. About 1/3 received the drugs inappropriately: impaired memory; depression without psychotic features; indifference to surroundings; insomnia; anxiety; wandering; restlessness; uncooperativeness; unsociability.
6. Nearly 40% of the study population using antipsychotics regularly resisted taking medication or eating meals, made disruptive noises, disrobed in public, or threw food.
7. About 5% of recipients were considered improved; 85% no change; 10% deteriorated. There was no difference in effect between those receiving appropriate dosing for appropriate indications, and those receiving an excessive dose for inappropriate indications

DISCUSSION

1. "Our most important finding was the high level of antipsychotic prescribing in NHs."
2. About half of the Medicare NH residents who received antipsychotics took doses exceeding maximum levels, received duplicative therapy, or had inappropriate indications.
3. Most out-of-guideline prescribing was for memory problems, non-aggressive behavior, or depression without psychotic features.
4. Doses prescribed often exceeded guidelines.
5. "This study raises questions about the current uses of antipsychotics in NHs."

CONCLUSION

Use of antipsychotics in NHs is widespread. Most atypicals were prescribed outside prescribing guidelines, and used higher doses for indications for which there was no strong clinical evidence of benefit.

Failure to detect positive relationships between behavioral symptoms and antipsychotic therapy raises questions about appropriateness of prescribing.

Archives Int Med June 13, 2005; 165: 1280-85 Original investigation, first author Becky A Briesacher, University of Massachusetts, Worcester.

1 Clozapine Risperidone Olanzapine Quatrain Ziprasidone Aripiprazole
Older agents included haloperidol (*Haldol*) and chlorpromazine (*Thorazine*).

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When To Intervene? How To Intervene?

6-7 Thresholds For Normal Blood Pressure And Serum Cholesterol.

What is "normal" BP?. What is "normal" cholesterol? There is disagreement. In 1999 over 800 doctors wrote the director general of the WHO outlining fears that their new hypertension guidelines would result in increased use of antihypertension drugs at great expense, and for little benefit.

The simplistic linear structuring of many research questions, and the extrapolation of research results produce guidelines that make many doctors feel uneasy about the high proportion of patients who are being labeled as sick.

Primary care clinicians are aware of the adverse effects of undue medicalization. They tend to question the external validity (the application of trial results to individual patients seen in practice) of randomized controlled trials under experimental conditions. They also have to consider the costs of intervening to alter risk profiles of large numbers of healthy people. “The uneasiness is about primary prevention being conceived increasingly as a strategy implying individual risk identification and questionable labeling of disease.”

In 2003, European guidelines suggested a BP of above 140/90, and a cholesterol above 5mmol/L (193 mg/dL) as the appropriate thresholds for intervention (lifestyle and drug treatment). “The bottom line is that the doctor is expected to inform the patient that these measurements mean that he or she is at increased cardiovascular risk.” “A disease label is to be attached to the patient.”

In Norway, if this threshold for cholesterol and BP were to be applied at age 24, half the population would be identified as being at increased risk. At age 49, the proportion is raised to 90%. As many as 75% of the total population would be identified as being at risk.

Issues to be considered:

1) The potential benefits for treated patients become less at lower risk levels. The number needed to treat to benefit is increased. The rates of adverse effects (of drug treatment) remain the same. Adverse effects tend to be under-reported and under-published.
2) Evidence for the long-term effectiveness of treatment is lacking. Data from short-term studies are being extrapolated over the whole of the remaining lifespan.
3) We have limited evidence on the effects of preventive drug treatment when several drugs are used to treat different risk factors simultaneously.
4) We have far too little understanding of the psychological impact and the wider health consequences of being labeled at risk.
5) Overall costs to society may be tremendous.

BMJ June 25, 2005; 330: 1461-62 Editorial, first author Steiner Westin, Norwegian University of Science and Technology, Trondheim.

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No Evidence Of Superiority For A Calcium Channel-Blocker, Or An ACE Inhibitor Compared With A Thiazide-Type Diuretic as Initial Therapy

6-8 CLINICAL OUTCOMES IN ANTIHYPERTENSIVE TREATMENT OF TYPE 2 DIABETES, IMPAIRED FASTING GLUCOSE CONCENTRATION, AND NORMOGLYCEMIA

The Antihypertensive and Lipid-lowering Treatment to prevent Heart Attack Trial (ALLHAT)

This sub-set of the ALLHAT trial determined whether treatment with a calcium-blocker, or an angiotensin-converting enzyme inhibitor would decrease clinical complications as compared with a thiazide-type diuretic in patients with type 2 diabetes (**DM**), impaired fasting glucose **(IFG**), and normoglycemia **(NG**). The double-blind

randomized, controlled trial entered over 31 000 adults with hypertension, all over age 55. All had at least one additional risk factor for coronary heart disease. (Ie, a high-risk group.)

Patients were randomized to *first* step therapy with: 1) chlorthalidone, 2) amlodipine, or 3) lisinopril.

Primary outcome measures were fatal coronary heart disease and non-fatal myocardial infarction.

Results:

A. There were no significant differences between the 3 drugs in relative risks for the primary outcomes in patients with DM or NG.

B. A significantly higher risk was noted for the primary outcome in IGF patients assigned to amlodipine vs chlorthalidone.

C. Stroke was more common in NG patients assigned to lisinopril vs chlorthalidone.

D. Heart failure was more common in DM and NG patients assigned to amlodipine or lisinopril vs chlorthalidone.

Conclusion: There was no evidence of superiority for treatment with a calcium channel-blocker, or an ACE inhibitor compared with a thiazide-type diuretic during *first-step* antihypertension therapy in DM, IFG, or NG.

Archives Int Med June 27, 2005; 165: 1401-09 Original investigation by the ALLHAT Collaborative Research Group, first author Paul K Whelton, Tulane University Health Sciences Center, New Orleans.

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Likely To Produce Clinically Important Pain Relief.

6-9 EFFICACY AND SAFETY OF OPIOID AGONISTS IN THE TREATMENT OF NEUROPATHIC PAIN OF NON-MALIGNANT ORIGIN A Systematic Review.

Peripheral neuropathic pain **(NP)** includes diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and phantom pain after amputation. Central neuropathic pain includes post-stroke pain, pain of multiple sclerosis, and post-spinal cord injury pain.

The main clinical characteristic of NP is continuous or intermittent spontaneous pain, typically described as burning, aching, or shooting; and abnormal sensitivity of the painful site to normally innocuous stimuli such as light touch (allodynia). Pharmacologic treatment has generally involved use of antidepressants, or anticonvulsants.

Effective pain relief is difficult to achieve. Use of opioids for NP is controversial. This is in part because studies have been small, have yielded equivocal results, and have not established long-term efficacy and safety. There have been concerns about adverse effects: potential for abuse and addiction, hormonal abnormalities, dysfunction of the immune system, and paradoxical hyperalgesia.

This systematic review assessed the efficacy and safety of opioids for treatment of NP.

Conclusion: Short-term studies (< 24 hours) provided equivocal evidence of efficacy. Intermediate-term studies (8 to 56 days) demonstrated significant efficacy. Reported adverse effects were common, but not life-threatening.

STUDY

1. Literature search extracted data from randomized, controlled trials of opioid treatment of NP of any etiology. Drugs included morphine, fentanyl, meperidine, and oxycodone.
2. Excluded trials in which drugs other than opioid agonists were combined with the opioid. No trials of epidural or intrathecal opioids were included.
3. Fourteen trials met inclusion criteria for short-term use (< 24 hours).
4. Eight trials met inclusion criteria for intermediate-term use (range 8 to 56 days; median = 28 days).

RESULTS

1. In all short-term trials, opioids were superior to placebo, but reached statistical significance in only 3 of 14. The overall difference in pain intensity was 16 points lower on a visual analogue 0 to 100 scale
2. All 8 intermediate trials demonstrated efficacy for reducing pain. A meta-analysis of 6 of the trials showed mean post-treatment visual analogue scale scores of pain intensity after opioids to be 14 units lower (compared with placebo) on a scale of 0 to 100.
4. The most common adverse effects were nausea, constipation, drowsiness, vomiting, and dizziness. (NNT to harm one patient = 4 to 7.)

DISCUSSION

1. "We conclude that intermediate-term opioid treatment has a beneficial effect over placebo for spontaneous neuropathic pain for up to 8 weeks of treatment and that the magnitude of this opioid effect in nearly a 14-point difference in pain intensity at study end compared with placebo. "
2. A benefit was achieved with low to moderate doses. Higher doses may have the potential to produce a greater effect.
3. Is an average decline of 14 points on a 100-point scale meaningful to patients? The mean initial pain intensity ranged from 46 to 69. A 14-point difference corresponds to a 20% to 30% reduction in pain.
4. Despite limited data, the meta-analysis showed similar responsiveness for pain of central and peripheral etiologies.
5. The trial did not address issues of addiction. It is reasonable to assume that the studies did not include individuals who might be potential abusers.
6. No consistent improvements in quality-of-life could be demonstrated.

CONCLUSION

Intermediate use (8 weeks or more) is likely to produce clinically important pain relief.
Reported adverse effects are common, but not life-threatening.

JAMA June 22/29 2005; 3043-52 Original investigation, first author Elon Eisenberg, Rambam Medical Center, Haifa, Israel.

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Donepezil May Delay Clinical Progression To Alzheimer's Disease

6-10 VITAMIN E AND DONEPEZIL (*ARICEPT*) FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT

Amnestic (memory loss) mild cognitive impairment **(MCI)** represents a transitional state between the cognitive changes of normal aging and the earliest clinical features of Alzheimer's disease **(AD).** Amnestic MCI refers to the subtype that has a primary memory component, either alone or in conjunction with other cognitive-domain impairments of insufficient severity to constitute dementia. About 80% of those who meet the criteria for MCI will have AD within 6 years.

The rate of progression from MCI to clinically diagnosable AD is 10% to 15% per year. This contrasts to a rate of 1% to 2% per year among normal elderly persons.

The presence of the APOE e4 alleles is associated with a more rapid rate of progression.

Preventing the progression of MCI to AD is likely to provide substantial benefit.

Oxidative damage accompanies AD. A previous large study reported that vitamin E could *delay* the time to important clinical milestones in patients with moderately severe AD. Cholinesterase inhibitors have been recommended for treatment of mild-to-moderate AD.

This study was designed to determine if vitamin E or the cholinesterase inhibitor donepezil could delay the clinical diagnosis of AD in patients with MCI.

Conclusion: Vitamin E produced no benefit. Donepezil was associated with a lower rate of progression during the first 12-24 months. After 3 years, progression to AD did not differ from those receiving placebo.

STUDY

1. Double-blind trial enrolled 769 subjects (mean age = 73) with amnestic MCI of insidious onset and gradual progression of impaired memory. APOE carriers—55%
2. Criteria for diagnosis of amnestic MCI:
   A. A delayed-recall score of 1.5 to 2 standard deviations below the education-adjusted norm.
   B. A clinical dementia rating of 0.5.
   C. A score of 24 to 30 on the Mini-Mental State Examination.
   D. Age 55 to 90.
3. Baseline means:
   Cognitive score = 18 (range 0 to 85, higher scores indication poorer function.)
   MMSE score = 27 (range 0 to 30)
   Score for activities of daily living = 46 (range = 0 to 53, higher scores indicating better function.)
4. Randomized to daily doses of:
   A. 2000 IU vitamin E, or
   B. 10 mg donepezil, or
   C. Placebo.
5. Primary end point = time to development of possible or probable AD. Follow-up = 3 years.

RESULTS

1. Over 3 years, 212 (28%) developed possible or probable AD. Overall progression to AD was 16% per year.
    1) Vitamin E group vs placebo: No significant differences in progression to AD at any point over the 3 years, including carriers of the APOE e4 allele. (Hazard ratio = 1.02)
    2) Donepezil group vs placebo:
        A. At 12 months, this group had a reduced likelihood of progression (16 subjects vs 33). There was a relative reduction in risk of progression of 56% at one year and 36% at two years.
        B. Over 3 years, no significant differences in progression to AD (63 subjects vs 73). (Hazard ratio = 0.80)
        C. APOE e4 carriage was a major predictor of more rapid progression to AD. Among carriers of APOE e4 alleles, the benefit of donepezil was evident throughout the 3 years of follow-up.
2. Memory, language, global measures of cognition, disease severity, and stage of dementia all paralleled the overall treatment effect of donepezil
3. Adverse events in donepezil: muscle cramps; GI symptoms; sleep disturbance. 29% discontinued treatment (more than in the other 2 groups).

DISCUSSION

1. Over 3 years, there were no statistically significant differences in the probability of progression to AD between donepezil, vitamin E, and placebo.
2. Although vitamin E had no effect at any time, donepezil demonstrated a reduced likelihood of progression to AD in the first 12 and 24 months.
3. “These results suggest that donepezil may delay clinical progression to Alzheimer’s disease.”
4. “The observed relative reduction in the risk of progression of 56% at one year and 36% at two years in the entire cohort is likely to be clinically significant.”
5. “Although our findings do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment, they could prompt a discussion between the clinician and the patient about this possibility.”
6. The presence of the APOE e4 alleles was highly predictive of progression to AD. Most of the treatment effect of donepezil occurred among APOE e4 carriers. “However, there are insufficient data to recommend genotyping in persons with mild cognitive impairment.”

CONCLUSION

Donepezil may delay the clinical diagnosis of AD, but only for the first year.

The benefit of donepezil was more prominent among carriers of the APOE e4 gene.

NEJM June 9, 2005; 352: 2379-88 Original investigation by the Alzheimer's Disease Cooperative Study Group, first author Ronald C Petersen, Mayo Clinic College of Medicine, Rochester, Minn.

An editorial in this issue (pp 2439-41 by Deborah Blacker, Harvard Medical School, Boston, Mass. comments:

"The implications of this study for primary care medicine and for public health are enormous." The clear-cut negative findings of vitamin E are especially noteworthy.

The findings for donepezil are much less clear.

MCI is a transition state between normal aging and dementia (for Alzheimer's disease in particular), one in which cognitive deficits are present, but function preserved. In clinical settings, the term is often used to describe patients who present with memory loss, but do not have dementia. Even when defined carefully, MCI is a heterogeneous category that includes some persons with memory changes of normal aging, some with non-progressive cognitive defects, some with prodromal AD, and some with prodromal forms of other neurodegenerative dementias. Only those on a course toward AD are likely to benefit from AD-specific interventions.

There is evidence that pathological changes of AD are already well established in the brain in a substantial fraction of those with MCI. Attempts to prevent progression are more accurately viewed as early intervention.

Donepezil is a widely used cholinesterase inhibitor with limited clinical benefits for treatment of AD. Use is sometimes equated with a 6-month delay in progression compared with placebo.

Vitamin E is widely used for all types of patients with AD because of its low cost and perceived safety. It is also widely used for primary prevention by people with normal cognition.

MCI can now be measured and studied. . . "Which is no small feat for a syndrome that was delineated less than a decade ago".

What lessons does the study offer?

1) Symptoms of memory loss in older persons should be taken seriously. They may represent the beginning of AD. This may be an important clinical measure once more effective treatments become available.
2) Donepezil may offer some benefit, although limited and transient.
3) Vitamin E is of no benefit in delaying onset of AD.

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In Modestly Overweight Persons, Reduction In Weight May Lower Risk Of Developing Hypertension.

6-11 WEIGHT LOSS IN OVERWEIGHT ADULTS AND THE LONG-TERM RISK OF HYPERTENSION: The Framingham Study

Excess body weight is the strongest known risk factor for hypertension. Its adverse effects begin in childhood.

Obesity is notoriously difficult to treat. The great majority of patients who lose weight subsequently regain it.

In patients with hypertension, weight loss, whether alone, or in combination with medication, has a beneficial effect on BP control.

Previous analyses of overweight subjects from the Framingham Study showed that change in weight was associated with a linear change in BP, and sustained weight loss was associated with a 30% reduction in the incidence of type 2 diabetes.

The goal of this study was to estimate the effects of both the amount on weight loss and the persistence of weight loss on the risk of incident hypertension among already obese adults. (*Primary prevention.)*

Conclusion: A modest weight loss, particularly when sustained, substantially lowered the long-term risk of developing hypertension.

STUDY

1. Evaluated weight loss among over 1200 overweight (BMI over 25) non-hypertensive subjects in a group of patients aged 30-49, and another group age 50-65. None were hypertensive at baseline.
2. Characteristics of subjects age 30-49 (means) at baseline:
   Age = 27 BMI = 27 BP = 124/80
3. Characteristics of subjects age 50-65 (means) at baseline:
   Age = 52 BMI = 28 BP = 124/79
   (*Note—these subjects were not considered obese; this degree of elevation of BMI is extremely common.)*
4. Classified subjects according to the amount of weight loss over 4 years:
   1) Weight loss less than 1.8 KG
   2) Loss 1.8 to 3.6 kg.
   3) Loss 3.6 kg to 6.8 kg.
   4) Loss over 6.8 kg.
4. Also classified weight loss according to whether it was sustained during the next 4 years.
5. Determined onset of hypertension over the years (up to 48 years).

RESULTS

1. After multiple adjustments, weight loss of 6.8 kg (18 pounds) or more led to a 28% reduction in risk of developing long-term hypertension in younger subjects, and a 37% reduction in older subjects.
2. If the weight loss was sustained over the years, the risks of developing hypertension were reduced by 22% and 26%.

DISCUSSION

1. For primary prevention of hypertension in modestly overweight persons, there may be significant long-term reduction in onset of hypertension related to modest weight. (*Primary prevention*)
2. Obesity is associated with higher levels of insulin resistance, hyperinsulinemia, rises in cardiac output, increases in cholesterol and triglycerides, and increased sympathetic nervous system activity. Most of these changes have been associated with increases in BP. “In recent years, there has been a great deal of focus on the roles of hyperinsulinemia and insulin resistance in the development of hypertension.”
3. “The results of this study suggest that at least 15% of the cases of hypertension in overweight middle-aged

adults and 22% of the cases occurring in overweight older adults could be prevented by a modest amount of sustained weight loss."

Archives Int Med June 13, 2005; 165: 1298-2005 Original investigation, first author Lynn L Moore, Boston University School of Medicine, Mass.

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Treatment Reduced Serious Perinatal Morbidity In Infants And May Improve The Woman's Health-Related Quality Of Life.

6-12 GESTATIONAL DIABETES MELLITUS; Effect Of Treatment On Pregnancy Outcomes.

Gestational diabetes mellitus **(GDM)** occurs in up to 9% of all pregnancies. It is associated with substantial maternal and perinatal complications. Neonatal complications include macrosommia, shoulder dystocia, birth injuries, bone fractures, nerve palsies, and hypoglycemia. Long-term adverse health outcomes among infants born to mothers with GDM include sustained glucose intolerance, subsequent obesity, and impaired intellectual achievement.

For the mother, GDM is a strong risk factor for type 2 diabetes and may be related to increased risk of anxiety, depression, and impaired health status.

This study asked . . Does screening and treatment for GDM reduce these risks?

Conclusion: Treatment of GDM reduced serious perinatal morbidity in infants and may improve the woman's health-related quality of life.

STUDY

1. Enrolled 1000 women who were between 16 and 30 weeks pregnant.

   All had onset or recognition of GDM during the present pregnancy with:

   A. A positive 50-g oral glucose tolerance challenge test (glucose level one hour after glucose challenge of 140 mg/dL or more) *and*,

   B. A 75-g oral glucose tolerance test at 24 to 34 weeks in which the fasting plasma glucose was less than 140 mg/dL, two hour p.c. glucose was 140 to 198 mg/dL at. (Intermediate between the normal and diabetic response.

2. Women with more severe glucose intolerance were excluded.

3. Randomly assigned to:

   A. Intervention group: (n = 490)

      1) Ongoing care by obstetrical team.

      2) Individualized dietary advice taking into account the woman's pre-pregnancy weight, activity level, and weight gain.

      3) Instructions in self-monitoring glucose levels at least 4 times a day. Monitoring continued until achieving a fasting glucose of at least 63 mg/dL and no more than 99, and pre-prandial levels no more than 99, and 2-hour post-prandial no more than 126.

4) Insulin therapy with dose adjusted on the basis of glucose levels.

B. Routine care group: (N = 510)

Women and caregivers were not aware of their diagnosis of glucose intolerance of pregnancy. This care replicated clinical care in which screening for GDM is not available.

RESULTS

1. Infants:

A. Serious perinatal complications in infants were significantly lower in the intervention group (1% vs 4%). The NNT to prevent one serious outcome in infants = 34.

B. Birth weights were lower in the intervention group. (less likely to have macrosommia.)

C. No difference in rate of hypoglycemia requiring intravenous glucose.

2. Women:

A. Insulin therapy was given to 20 % in the intervention group *vs* 3% in the usual care group.

B. Rate of caesarean deliveries was similar.

C. Women in the intervention group gained less weight and had less risk for preeclampsia.

D. At 3-months postpartum, women in the intervention group had lower rates of depression and higher scores on quality-of-life.

DISCUSSION

1. Treatment of GDM reduced the rate of serious perinatal complications in infants.

2 “Our trial revealed an improved health-related quality-of-life among women in the intervention group, both during the antenatal period and three months after birth, together with a reduction in the incidence of depression after birth.”

3. Is it ethical to withhold the diagnosis of GDM as was done in the routine care group?

The authors defend their decision not to inform these women:

A. At the time of the study, there continued to be no conclusive evidence regarding the treatment of GDM. There were wide variations in clinical practice at the time.

B. Women in the non-intervention group received standard pregnancy care consistent with care in which screening for GDM is not routine.

CONCLUSION

Treatment of GDM in the form of dietary advice, blood glucose monitoring, and insulin therapy as required for glucose control, reduced the rate of serious perinatal complications without increasing the rate of caesarean delivery.

NEJM June 16, 2005; 352: 2477-86 original investigation, by the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group, first author Caroline A Crowther, University of Adelaide, Australia.

An editorial in this issue of NEJM, first author Michael F Greene, comments:

There is a worrisome rise in prevalence of GDM that is largely related to the increase in maternal obesity.

GDM is broadly defined as carbohydrate intolerance beginning, or first recognized, during pregnancy. It has been the subject of controversy for decades. The US Preventive Services Task Force, noting the absence of data, concluded that the evidence is insufficient to recommend for or against routine screening.

Evidence has remained largely observational.

"This study provides critical evidence that identifying and treating gestational diabetes mellitus can substantially reduce the risk of adverse perinatal outcomes without, at least in this trial, increasing the rate of caesarean delivery."

Of note: the glucose levels currently recommended by US organizations to identify GDM differ. Their accepted criterion is two or more values on a 100 g oral glucose tolerance test at or above:

Fasting 95 mg/dL

One hour 180

Two hours 155

Three hours 140

The target levels during treatment were similar **to those in the study.**

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The Test Could Be Used As An Initial Approach To Diagnosis.

6-13 IS PROTON PUMP INHIBITOR TESTING AN EFFECTIVE APPROACH TO DIAGNOSE GASTRO ESOPHAGEAL REFLUX DISEASE IN PATIENTS WITH NON-CARDIAC PAIN? A Meta-analysis

Non-cardiac chest pain **(NCCP)** is defined as recurrent episodes of retrosternal pain which lack cardiac abnormalities**.** NCCP is extraordinarily common, the annual prevalence estimated at above 25% of the population. These patients consume a large proportion of health care resources.

Gastro esophageal reflux disease (GERD) is the most common cause.

Endoscopy, 24-hour esophageal pH monitoring, and esophageal manometry are used to evaluate these patients. The sensitivity of endoscopy is limited because most patients have non-erosive GERD. Esophageal pH monitoring is invasive, costly, and often unavailable.

Patients with NCCP are often treated empirically and successfully with proton pump inhibitors.

Can proton pump inhibitors be used as a *diagnostic* test?

This study evaluated the overall accuracy of the test.

Conclusion: In primary care, the test could be used as an initial approach to diagnosis.

STUDY

1. This systemic review and meta-analysis included 6 randomized, placebo-controlled trials evaluating the accuracy of proton pump *vs* placebo testing in patients with NCCP and suspected GERD.
2. GERD was confirmed by endoscopy and/or 24-hour esophageal pH monitoring.
3. The trials included 220 patients. Prevalence of GERD among these patients with NCCP varied from

33% to 76%

4. Lansoprazole (*Prevacid*) and omeprazole (*Prilosec*) were most often the drugs used.
5. For each study, the authors calculated sensitivity and specificity using a cut-point of 50% or more relief of discomfort. (> 50% relief as judged by the patient was considered a positive test; < 50% a negative test.)

RESULTS

1. Results of the PPI test:

	GERD present	GERD absent
Positive test (> 50% relief)	80% (true positive)*	26% (false positive)
Negative test (< 50% relief)	20% (false negative)	74% (true negative test)**

(* sensitivity of the PPI test = true + % = 80%; ** specificity of the PPI test = true negative % = 74%)

2. Results of the placebo test:

Positive test (> 50% relief)	19% (true positive)***	23% (false positive)
Negative test (< 50% relief)	81% (false negative)	77% (true negative test)****

(*** sensitivity of placebo test =19%; **** specificity of placebo test = 77%)

3. Thus 80% responded favorably to PPI *vs* 19% to placebo. (The authors considered this difference to be discriminative and to indicate that the PPI test had "acceptable" sensitivity and specificity for diagnosing GERD.)

DISCUSSION

1. "Our results show that the sensitivity of the PPI test was significantly higher than that for placebo; whereas the specificity was almost the same between both groups."
2. Treatment with PPIs and placebo showed similar effects (26% and 23%) on improving NCCP symptoms in patients without GERD, indicating a possible placebo effect. "The considerably higher placebo effect is not uncommon in patients with functional bowel disorders and not surprising in patients with non-GERD-related NCCP."
3. "The accuracy of a diagnostic test should be evaluated by comparing its results with a gold (reference) standard. However, this is not available for the diagnosis of GERD. The sensitivity of symptom evaluation falls short of a gold standard.
4. The sensitivity of the PPI test seems to be related to the duration of the treatment. Extending treatment to 4 weeks increases sensitivity.
5. Sensitivity and specificity can be increased if reflux symptoms are also evaluated.
6. There are differences in the definition of NCCP, the type and dosage of PPI used, the washout period, degree of blinding, execution of the test, and reference standard for diagnosing GERD. "Biases may exist."

CONCLUSION

The use of PPI as a diagnostic test for detecting GERD in patients with NCCP has an “acceptable” sensitivity and specificity and could be used as an initial approach by primary care physicians to detect GERD in selected patients with NCCP.

Archives Int Med June 13, 2005; 165: 1222-28 Original investigation, a meta-analysis, first author Wei Hong Wang, Peking University First Hospital, Beijing, China.

The authors suggest the sensitivity and specificity of the PPI test is “acceptable”. What is “acceptable”.?

Acceptability of a test may be judging the pre-test likelihood of the disease being present modified by the likelihood ratios of the test:

1) Assume that, in your clinical judgment based on symptoms, signs, and knowing the patient’s clinical history and personality, you believe there is a 50% likelihood that her NCCP is due to GERD. (The pretest likelihood = 50%)
2) A positive test—in this example, relief of discomfort of 50% or more—can be either a true positive (80%) or a false positive (20%).

   The positive likelihood ratio is simply the ratio between true positive tests and false positive tests: 80/20 = 3.1.

   In this example, if we assume the pretest probability that GERD is present, is 50%, a positive test will increase the probability that the disease is present. A nomogram is used to calculate the resultant post-test probability. In this example the positive test increased the probability that the disease is present from 50% to 75%.
3) A negative test—in this instance relief of discomfort of less than 50%--can be either a false negative (20%) or a true negative (74%)

   The negative likelihood ratio is simply the ratio between false negative tests (20%) and true negative tests (74%): 20/74 = 0.27

   Using the nomogram again, the negative test lowered the probability that the disease is present from 50% to 21%

If other clinical markers were present (eg, reflux symptoms) our clinical judgment would likely increase the pre-test probability that GERD is present. The post-test probability would then be higher.

Both the positive likelihood ratio and the negative likelihood ratio were modestly helpful in this study. If the positive likelihood ration had been 10, the disease would be effectively confirmed. If the negative likelihood ratio were 0.1, the disease would have been effectively ruled out.

To obtain a nomogram and an excellent description of likelihood ratios go to GOOGLE and access “likelihood ratios”, presented by the Centre for Evidence-Based Medicine.

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May Reduce Risk Of Development Of PMS.

6-14 CALCIUM AND VITAMIN D INTAKE AND RISK OF INCIDENT PREMENSTRUAL SYNDROME

Up to 90% of premenopausal women regularly experience affective and /or physical symptoms before the onset of menses. Up to 20% experience symptoms that meet the clinical definition of premenstrual syndrome **(PMS),** a disorder characterized by moderate to severe symptoms which substantially interfere with normal activities and interpersonal relationships. Symptoms are limited to the luteal phase of the cycle, and abate shortly after onset of menses.

Oral contraceptives, gonadotropin-releasing hormone agonists and serotonin reuptake inhibitors have been used as therapy. They have adverse effects and can be expensive.

Alternatives such as dietary supplements are being evaluated.

Several studies have suggested that calcium and vitamin D levels are lower in women with PMS, and that calcium supplementation may prevent the initial development of PMS.

This study asked: Would calcium and vitamin D prevent the *initial* development of PMS?

Conclusion: A high intake of dietary calcium and dietary vitamin D may reduce risk of development of PMS.

STUDY

1. This case-control study was nested within the large prospective Nurses' Health Study. Participants were a subset of women age 27 to 44 (mean = 35). All were free of PMS at baseline (1991).
2. Cases: 1057 women who developed PMS over a 10-year follow-up.
3. Controls: 1968 women who reported no diagnosis of PMS and no, or minimal, menstrual symptoms.
4. Determined dietary and supplemental intakes of calcium and vitamin D by periodic questionnaires.

RESULTS

1. After adjustment for age, parity, and smoking status, and other risk factors, women in the highest quintile of total vitamin D intake (median of 706 IU) had a relative risk of new-onset PMS of 0.59 compared with those in the lowest quintile (median of 112 IU). Benefit was associated with vitamin D from food. Supplemental vitamin D did not seem to be associated with risk.
2. The intake of calcium from food sources was also inversely related to onset of PMS; compared with women with a low intake (median 529 mg/d), women with the highest intake (median 1283 mg/d) had a relative risk of 0.70. Calcium from supplements was not associated with risk—only calcium from food.
3. The intake of skim or low-fat milk was also associated with a lower risk. Participants consuming 4 servings/d or more of skim or low-fat milk had a RR of developing PMS of 0.54 compared with women who consumed 1 serving or less per week.
4. Whole milk intake was associated with a modest *increase* in development of PMS

DISCUSSION

1. "Findings from our nested case-control study suggest that a high dietary intake of vitamin D and calcium

may lower the risk of *incident* PMS." There was a significantly lower risk of developing PMS in women with a high intake of vitamin D and calcium from food sources such as skim or low-fat milk, fortified orange juice, and low-fat dairy foods such as yogurt. These dietary (not supplemental) intakes correspond to approximately 1200 mg of calcium and 400 IU of vitamin D daily.

2. The authors state that the data regarding supplemental calcium are not firm..
3. Why should calcium be protective? The authors suggest that calcium and vitamin D may influence development of PMS through a relationship to endogenous estrogens and parathyroid hormones.
4. This may be an added inducement for women who wish to reduce their risk of osteoporosis.

CONCLUSION

A high intake of dietary calcium and dietary vitamin D may reduce the risk of developing PMS.

Archives Int Med June 13, 2005; 165: 1246-52 Original investigation, first author Elizabeth R Bertone-Johnson, University of Massachusetts, Amherst.

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Hope For Reducing The Prevalence Of This World-Wide Scourge.

6-15 BASIC SCIENCE GUIDELINES DESIGN OF NEW TB VACCINE CANDIDATES

A number of new vaccine candidates are being entered into phase 1 clinical trials.

The BCG (Bacillus Calmette-Guerlin) was developed almost 100 years ago. It is still being used in many parts of the world, It is an attenuated live vaccine made from a strain of the bacterium that causes TB in cattle (*Mycobacterium bovis*). Its efficacy in protecting individual against TB is variable.

Attempts are being made to improve the existing BCG vaccine. One approach is to add an extra copy of the gene for a major secretory protein of an M tuberculosis antigen. The standard BCG vaccine contains this gene, the extra copy causes the antigen to be made in greater amounts. This results in a stronger immune response.

Another approach is to add a gene from *Listeria monocytogenes*. This stimulates a vigorous CD8 T-cell response in addition to the CD4 response. CD8 T-cells also contribute to protection against M tuberculosis.

Another approach is to prime with a BCG vaccine and then boost the immune response with a different TB vaccine—either a subunit vaccine or a live vaccine.

Still another, the furthest along in clinical trials is a viral vector (a modified vaccinia virus) to which has been added an antigen similar to that in the BCG vaccine. It is given as a booster to persons who have received the BCG vaccine. It . . ."Produces an overwhelming CD4 T-cell response". This vaccine is presently being tested for use in individuals who are latently infected with TB. If successful, this should have a much more immediate impact on the burden of morbidity and mortality.

Others are being investigated. Safety is the main concern.

JAMA June 8, 2005; 293: 2704-05 "Medical News and Perspectives" editorial by M J Friedrich, JAMA Staff.

While this is not a practical point, it was enticing enough for me to abstract.