# PRACTICAL POINTERS

## FOR
# PRIMARY CARE

## ABSTRACTED MONTHLY FROM THE JOURNALS

# OCTOBER 2006


**OBESITY MANAGEMENT—DRUG TREATMENT**

**OBESITY MANAGEMENT—SURGERY**

**A NEW EFFECTIVE TREATMENT OF MACULAR DEGENERATION**

**SHOULD WE USE A NON-APPROVED DRUG WHEN PATIENTS CANNOT AFFORD THE APPROVED DRUG?**

**DO OPIATES AFFECT THE CLINICAL EVALUATION OF PATIENTS WITH ACUTE ABDOMINAL PAIN?**

**THE FERRITIN ASSAY IS PREFERRED TO DIAGNOSE IRON DEFICIENCY**

**IN MEN WITH HEALTHY LIFESTYLES, MODERATE ALCOHOL CONSUMPTION MAY REDUCE RISK OF CHD**

**USE OF ATYPICAL ANTIPSYCHOTIC DRUGS FOR ALZHEIMER'S DISEASE**

**CT SCANNING ASYMPTOMATIC SMOKERS FOR DIAGNOSIS OF STAGE I LUNG CANCER**

**ORAL RENIN INHIBITORS—A PREVIEW**

**THE ANGIOTENSINOGEN-ANGIOTENSIN I-ANGIOTENSIN II-ALDOSTERONE CASCADE**



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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

**HIGHLIGHTS** condenses the contents of studies, and allows a quick review of pertinent points of each article.

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***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.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents 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.

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# HIGHLIGHTS AND *EDITORIAL COMMENTS* OCTOBER 2006

***Obesity Drugs Can Increase Weight Loss By About 4 To 6 Kg Above What Can Be Achieved By Diet Alone.***

**10-1 OBESITY—DRUG TREATMENT**

"Despite the availability of evaluated and approved obesity drugs, and even though some patients will have failed to lose weight after non-drug treatment—doctors have been reluctant to prescribe drugs." This may because of memories of past adverse effects of amphetamine and amphetamine-like drugs.

The use of obesity drugs should follow the principles of any other therapeutic area—that is, they may be prescribed after assessment of the potential benefits and risks (both clinical and economic).

Effective treatment, including drugs when needed, must be life long and focused on maintenance of weight loss in a similar fashion to the effective treatment of hypertension and diabetes. Drugs are logical treatment, not just for weight loss induction, but for long term weight loss maintenance.

Overall benefits of existing drugs has been favorable in terms of symptoms, risk factors, and diabetes prevention.

The review discusses two obesity drugs: orlistat and sibutramine.

Read the full abstract.

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*I believe vitamin supplementation should be prescribed for patients attempting to lose weight, including those on drugs.*

***"The Safety And Efficacy Of Surgery Has Improved Remarkably"***

**10-2 OBESITY MANAGEMENT – SURGERY**

Obesity surgery ("bariatric", or "behavioral" surgery) is a successful validated, and legitimate treatment and needs to be considered in some circumstances."

Twelve clinical points. Read the full abstract

***"MIRACULOUS"***

**10-3 A VERY EFFECTIVE TREATMENT FOR NEOVASCULAR MACULAR DEGENERATION**

Age related macular degeneration is a complex disorder which begins decades before a patient becomes symptomatic. In about 10% of patients with the condition, a derangement of vasculature beneath Bruch's membrane leads to a new growth of blood vessels from the capillaries beneath the membrane into the subretina. This neovascular complication damages the retina. It is responsible for the vast majority of cases of legal blindness attributable to this disease.

Vascular endothelial growth factor (VEGF; a protein) has emerged as an important molecule in the angiogenic process. Several recombinant monoclonal antibodies (ranibizumab is the latest FDA approved drug) have been designed to inhibit action of this growth factor. Patients receiving intra-*vitreous* injection of ranibizumab monthly over 2 years gained, on average, more than one line of visual acuity. Controls lost vision. Ranibizumab was much more effective than photodynamic therapy.

The efficacy of this treatment has been termed “miraculous”.

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*While this application is not directly applicable to primary care, primary care clinicians should be aware of it.*

***Should We Give An Off Label Drug When The Patient Cannot Afford The Approved Drug?***

**10-4 RANIBIZUMAB, BEVACIZUMAB, AND TREATMENT OF MACULAR DEGENERATION—THE PRICE OF SIGHT**

Ranibizumab (*Lucentis*; Genentech) is a fragment of a recombinant monoclonal antibody that binds to, and inhibits, vascular endothelial growth factors in and beneath the retina. It is injected into the vitreous monthly. Treatment is likely to be required indefinitely It presently costs about $2000 for a single dose.

A precursor recombinant antibody, bevaci-zumab (*Avastin;* Genentech), given intravenously, has been approved for treatment of metastatic cancer of the colon and rectum. It is now being given intravitreously (off label) in smaller doses at a much lower cost. It has not yet been directly compared with ranibizumab. The benefit/harm ratio compared with ranibizumab is not known. The cost differential is important.

***This May Save The Patient Hours Of Pain.***

**10-5 DO OPIATES AFFECT THE CLINICAL EVALUATION OF PATIENTS WITH ACUTE ABDOMINAL PAIN?**

Clinicians have traditionally withheld opiate analgesia from patients with acute abdominal pain until after evaluation by a surgeon. This is out of concern that analgesia may alter the physical findings, and interfere with diagnosis. Older textbooks of surgery historically discouraged opiate analgesia for patients with acute abdominal pain.

This systematic review included 12 placebo-controlled randomized trials of opioid analgesia (3 in children and 9 in adults). All reported changes in the history, physical examination, or diagnostic errors resulting in “management errors” due to opiate administration. Management errors were defined as performance of unnecessary surgery, or failure to perform necessary surgery in a timely fashion.

Changes in physical examination: Studies showed trends toward increased risks of altered findings on the abdominal examination due to opiate administration. Relative risk of altered findings (opiates vs placebo) = 1.51. (95% confidence interval (CI) = +0.85 to +2.69)

Management errors as a marker for important changes in the physical examination: Opiates had no significant association with management errors. (RR = +0.3% absolute increase; (CI = -4.1% to + 4.7%). [“The magnitude of this nonsignificant increase in incorrect decisions is very small. If it had been significant, 333 patients would need to receive opiates to result in one management error attributed to the analgesia.” “These data are also compatible with fewer management errors among patients receiving opiates.” Across all trials, with adequate analgesia, opiate administration may be associated with a non-significant absolute *decrease* in risk of management errors.

The evidence suggests that administration of opiates does not substantially alter the history of the illness.

“Given the humane duty of physicians to relieve pain and the totality of the available evidence, clinicians should administer analgesia unless further studies document adverse events directly attributable to opiates.”

***"The Ferritin Assay Provides A Simple Method Of Discriminating Between Iron Deficiency And Anemia Of Chronic Inflammation"***

**10-6 INVESTIGATING IRON STATUS IN MICROCYTIC ANEMIA**

To diagnose iron deficiency, measurement of ferritin is superior to iron and iron binding capacity or transferrin saturation. Elderly patients with anemia require a ferritin assay in order to establish whether iron deficiency is present.

Ferritin greater than 100 ug/L rules out iron deficiency. Under 15 ug/L rules in iron deficiency. The probability of iron deficiency remains high until the ferritin level is greater than 40 for the general population, and greater than 70 for those with chronic inflammation or liver disease.

MCV over 95 fL rules out iron deficiency. A low MCV (less than 85 fL) does not prove iron deficiency (especially in the elderly and those with inflammatory diseases). In anemic patients, the probability of iron deficiency increases with decreasing MCV, but no specific cut-off value can be used. About 20% of elderly patients with a MCV of under 75 fL will *not* have iron deficiency. They will most likely have the anemia of chronic inflammation. "Microcytic anemia alone is not sufficient to diagnose iron deficiency."

Ten clinical points. Read the full abstract.

***Is A Glass Of Wine With Dinner Part Of A Healthy Lifestyle?***

**10-7 ALCOHOL CONSUMPTION AND RISK FOR CORONARY HEART DISEASE IN MEN WITH HEALTHY LIFESTYLES.**

This study considered the effect of long-term moderate alcohol consumption on incidence of MI in over 8800 men who consistently reported healthy lifestyles. (Ie, alcohol in addition to the healthy lifestyle.) All reported 4 healthy lifestyle behaviors: 1) body mass index less than 25, 2) moderate to vigorous activity for 30 minutes or more daily, 3) not smoking, and 4) a high intake of vegetables, fruits, cereal fiber, fish, chicken, nuts, soy, and polyunsaturated fat. And, low consumption of trans fat, and red and processed meats.

Over 16 years of follow-up, determined incidence of non-fatal MI, and fatal coronary heart disease according to reported average daily intake of beer, wine, and liquor.

Hazard ratios for MI (multivariate adjusted) of average daily intake of alcohol (g per day) compared with abstention:

| 0 | 0.1 to 4.9 | 5.0 to 14.9 | 15 to 29.0 | 30 and over. |
|---|---|---|---|---|
| 1.00 | 0.92 | 0.52 | 0.32 | 0.70 |

(In absolute numbers, the differences between groups were small.)

In this prospective analysis of men with healthy lifestyles, moderate alcohol consumption was associated with a lower risk for MI, with the lowest risk in men who drank an average of 5 to 30 g/d (approximately one half to 2 drinks).

The individual and societal complications of heavy drinking are well known. "It is easy to understand why clinical guidelines encourage physicians and patients to concentrate on seemingly more innocuous interventions."

Because of the risks associated with high alcohol intake, clinical guidelines do not recommend alcohol consumption. We have other safer and proven interventions to lower risk of cardiovascular disease. However, healthy

behaviors are not mutually exclusive. Pursuit of exercise does not obviate the need for a healthy diet and smoking cessation.

Conclusion: In men with healthy lifestyles, already at low risk for MI, moderate alcohol intake was associated with lower risk for MI.

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*The apparently protective effect of moderate alcohol intake has been a frequent observation noted in the primary care literature. The evidence has been epidemiological, but consistent. Some epidemiologists even suggest that abstinence is a risk factor. Confounding factors cannot be excluded.*

*What should the primary care clinician advise? Other lifestyle factors certainly take priority.*

*For people who already drink, I believe we may advise that a glass of wine with dinner, may be slightly protective. Most clinicians would not prescribe it as the sole factor to reduce risk. I would not prescribe it de-novo. The other lifestyle factors, especially smoking, are more important.*

***"A Limited, But Sometimes Necessary Role"***

**10-8 EFFECTIVENESS OF ATYPICAL ANTIPSYCHOTIC DRUGS IN PATIENTS WITH ALZHEIMER'S DISEASE**

Psychotic symptoms affect more than half of patients with Alzheimer's disease (**AD**). Second generation (atypical) antipsychotic drugs are widely used in treatment.

This trial followed over 400 patients (mean age 78) with AD. All were ambulatory and living at home or in an assisted-living facility. All had delusions, hallucinations, aggression, or agitation. Symptoms were severe enough to disrupt functioning.

Patients were randomized to: 1) olanzapine (*Zyprexa*); 2) risperidone (*Risperidal*), or 3) placebo.

Eighty two % of patients discontinued the initially assigned medication during the 36-week follow-up; 18% continued.

Discontinued assigned treatment due to intolerability: olanzapine 24%; risperidone 18%; placebo 8%.

At least minimal improvement in Clinical Global Impression of Change scale at 12 weeks: olanzapine 32%; risperidone 29%; placebo 21%. (Not statistically significant.)

Both olanzapine and risperidone were equally effective and were superior to placebo in treating behavioral problems. The benefit was limited to a subgroup of patients who tolerated the drugs.

Flexible dosing (as used in this study) ensures one of the core principles of geriatric pharmacology "Start low and go slow, but go". Clinicians should start a drug at a dose at the lower end of the plausible therapeutic index and then increase the dose until there is efficacy or intolerable side effects

Conclusion: These results suggest that these drugs have a limited, but sometimes necessary role in the care of patients with AD. Although the atypical antipsychotic drugs were more efficacious than placebo, adverse effects limited their overall effectiveness.

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*The FDA label for antipsychotic medications states they are not approved for treatment of dementia-related psychosis. They display a "black box" warning—"Elderly patients with dementia-related psychosis are at increased risk of death compared with placebo."*

*What should the primary care clinician do? I believe many primary care clinicians who care for difficult AD patients will prescribe these drugs despite the FDA warning, realizing that many patients will not tolerate the drug. Careful assessment of individual response is a key. Care to treat the patient first, and not to primarily benefit the caregiver or nursing staff.*

*Note that about 20% of patients in the trial responded and were able to continue the drug. The authors do not state that these drugs should not be used, only that they may not benefit and may be associated with adverse effects which precludes their continuation.*

*I believe the core principles of geriatric pharmacology "Start low and go slow" applies to almost all drugs used long-term.*

***Should Primary Care Clinicians Advise Screening For Their High-risk Patients?***

**10-9 SURVIVAL OF PATIENTS WITH STAGE I LUNG CANCER DETECTED ON CT SCREENING**

Screened over 31 000 asymptomatic persons (age 40 to 86) at high risk of lung cancer (**LC**)—the great majority because of a long smoking history (median 30 pack-years).

At the first screen, CT was positive for at least one non-calcified nodule in 13%. Of these, further study (including follow-up CT and biopsy) revealed cancer in 10%. The overall presence of cancer was 1.3% of the entire first-screen cohort.

Over 27 000 subjects negative for LC on the first screen then underwent annual CTs. In this cohort, the CT was positive for a non-calcified nodule in 5%. Of these 5% were cancerous (0.3% of the 27 000).

The investigators *estimate* that the 10-year LC-specific survival for subjects with stage I LC undergoing resection within one month of diagnosis is 92%.

In the investigator's opinion, screening is cost effective, and is similar to the cost effectiveness of mammography.

Conclusion: Annual spiral CT screening for persons at high risk of LC because of smoking can detect LC that is curable.

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*This observational study does not determine the actual survival rate of patients screened and operated on for stage I LC vs subjects with stage I LC not operated on. The stated benefits in terms of survival are estimates. No randomized, controlled trial will be done to clarify this point.*

*The study does place some responsibility of primary care clinicians. It raises interesting questions:*

*1) Should primary care clinicians now routinely advise screening for their high risk patients? (As we do for mammography.) Or should we defer consideration until the patient raises his desire for screening?*

*2) In any case, we should consider the age and co-morbidities of the individual patient before going on to screen. As with prostate cancer, older patients may die of other causes.*

*3) If we advise screening, must we insist that the patient stops smoking, and require proof of cessation?*

*An imaginary scenario:*

*Doctor to patient: "You are now 60 years old. You have been smoking a pack of cigarettes daily for 40 years. You have no symptoms suggesting lung cancer. If you undergo screening, the chances of finding a suspicious nodule on the first screen are about 1 in 10. If such a nodule is found, you will be asked to enter a protocol with follow-up CT scanning and likely a biopsy. The chance of having a biopsy which shows lung cancer is 2%. There is then a 15% chance that the cancer will be too far advanced to operate on with any chance for cure.*

*Investigators estimate that, overall, 92% of patients detected by screening, and operated on within one month will survive for 10 years. But, there is no way of telling if the surgery will 'cure' you, or whether it will prolong your life. If you are not operated on, it is highly likely that you will die of the cancer.*

*If you do not stop smoking, the chance of recurrence of the cancer is high. I believe your best option is to stop smoking immediately."*

**10-10 ORAL RENIN INHIBITORS**

Inhibition of the renin-angiotensin system is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders.

The idea of blocking the *action* of renin on angiotensinogen (thus reducing levels of angiotensin I and angiotensin II) has existed for many years. Active research to produce an effective oral renin inhibitor has been conducted ever since.

This abstract discusses recent efforts to develop clinically effective renin inhibitors.

Read the full abstract.

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*Renin inhibition as a possible therapeutic measure is a new concept to me. This is not a practical point at this time. I abstracted the article because of its potential application and its general interest. This also gave me the opportunity to review the details of the A-AI-AII-A system. See the following. RTJ*

**10-11 THE ANGIOTENSINOGEN-ANGIOTENSIN I - ANGIOTENSIN II- ALDOSTERONE SYSTEM**

***Also Known As the Renin-Angiotensin System***

The angiotensinogen-angiotensin I-angiotensin II-aldosterone system (**A-AI-AII-A**) is a basic physiological system which helps maintain homeostasis. The complexity of the system is maddening. *(I prepared this simplified abstract for my own edification and enjoyment. RTJ)*

Inhibition of the system has been termed one of the most effective and important ways to intervene in the pathogenesis of cardiovascular and renal disorders including hypertension, left ventricular systolic dysfunction, acute myocardial infarction, and chronic renal disease (eg, diabetic). It also reduces risk when given to patients at high risk for cardiovascular disease.

This review includes the A-AI-AII-A cascade, the enzymes facilitating progress of the cascade, and mentions five drugs which block various stages of the cascade. See the full abstract.

# ABSTRACTS OCTOBER 2006

***Obesity Drugs Can Increase Weight Loss By About 4 To 6 Kg Above What Can Be Achieved By Diet Alone.***

**10-1 OBESITY—DRUG TREATMENT**

- "Despite the availability of evaluated and approved obesity drugs, and even though some patients will have failed to lose weight after non-drug treatment—doctors have been reluctant to prescribe drugs." This may because of memories of past adverse effects of amphetamine and amphetamine-like drugs.

- The use of obesity drugs should follow the principles of any other therapeutic area—that is, they may be prescribed after assessment of the potential benefits and risks (both clinical and economic).

- People who become obese have a lifelong tendency to defend their excess weight, and to continue to gain.

- Effective treatment, including drugs when needed, must be life long and focused on maintenance of weight loss in a similar fashion to the effective treatment of hypertension and diabetes.

- Starting treatment should always be regarded as a therapeutic trial, and stopped if weight loss in not apparent after one to two months.

- Current approaches to obesity management largely involve trying to treat all the additional symptoms, risk factors for future disease, and existing comorbidities without necessarily tackling the primary problem. Polypharmacy may be excessive. Obese persons often take 5 or more drugs, for components of the metabolic syndrome, plus symptomatic treatments such as bronchodilators, analgesics, and drugs for arthritis and angina. Insulin sensitizing agents (eg, metformin) are sometimes used to try to improve several obesity related risk factors. They rarely adequately improve the hazards and symptoms of obesity. But, polypharmacy may still be necessary.

- Temporary weight loss by liposuction lowers body weight, but does not establish energy balance at the lower weight. The metabolic syndrome is unaffected.

- An effective drug against obesity must reduce energy assimilation for food (without compensatory reduction in energy expenditure) or stimulate energy expenditure (without compensatory increase in food consumption), or both.

Principles of drug therapy:

- Weight loss: Many patients can achieve 5-10% weight loss in 3 to 6 months with lifestyle modifications and drug treatment. Current obesity drugs can increase weight loss by about 4 to 6 kg above what can be achieved by diet alone.
- Weight maintenance: Most patients who lose weight regain it. Drugs are logical treatment, not just for weight loss induction, but for long term weight loss maintenance. A reasonable long term target is to restrict weight gain.. Maintain weight loss (however achieved) 12 to 15 kg below baseline.
- Duration of treatment: It is logical to continue treatment as long as it is effective. Withdrawal will lead to weight gain. Current licensing limits duration of drugs to one or two years. Some "off label" trials show continuing benefit.
- Side effects and safety: Overall benefits of existing drugs has been favorable in terms of symptoms, risk factors, and diabetes prevention.

Drugs:

- Orlistat (*Xenical*; Roche): An intestinal lipase inhibitor taken 3 times a day. It generates malabsorption of 30% of dietary fat, leading to 5-10% loss of weight. In clinical trials, weight loss and related clinical benefits are largely maintained for up to 4 years. This is associated with reduction in all risk factors for coronary heart disease and diabetes. Steatorrhea will occur in patients who do not maintain a low fat diet. But gastrointestinal side effects are not necessary for effective weight loss because malabsorption of as little as 20 g of fat daily is usually asymptomatic and produces a daily energy deficit of 180 kcal.

- Sibutramine (*Meridia*; Abbott): Inhibits reuptake of nor-adrenaline and serotonin. This promotes prolonged satiety. It produces 5-10% weight loss in up to 70% of patients. It may be associated with an increase in heart rate and BP. These should be monitored. Controlled hypertension is not a contraindication.

- Rimonabant: A cannabinoid receptor antagonist. Activation of the cannabinoid receptor promotes eating and also promotes cardiovascular risk factors. Blockage produces weight loss and improves some risk factors. (*Not yet approved in the USA. RTJ*)

- Cost effectiveness: Drug treatment is considered cost effective.

BMJ October 14, 2006; 333: 794-97 Review article "ABC of Obesity" first author Mike Lean, Addenbrooke's Hospital, Cambridge, UK

Cost: *Xenical* 120 mg taken 3 times daily for one year = $2660.00

*Meridia* 10 mg once daily for 1 year = $1332.00; 15 mg taken once daily for 1 year = $1716.00

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## 10-2 OBESITY MANAGEMENT – SURGERY

- Obesity surgery ("bariatric", or "behavioral" surgery) is a successful validated, and legitimate treatment and needs to be considered in some circumstances."

- Compared with usual care, obesity surgery has recently been shown to reduce all cause mortality, mortality due to cancer, and cardiovascular morbidity.

- The safety and efficacy of surgery has improved remarkably.

- "Without understanding or accepting the severity of obesity and the risks of obesity surgery (or the "success" and risks of non-surgical alternatives) doctors and other health workers cannot advise patients in their choice of treatment.

- The goal of surgery is to prevent or reduce storage of excess energy as fat. The methods of surgery: 1) to reduce energy intake and absorption, and 2) to increase satiety (pleasant sense of fullness) or neutrality (neither hunger nor fullness), or 3) to increase unpleasant feelings of fullness.

- Key requirements for obesity surgery: 1) assessment of the patient to uncover motivational factors, 2) comprehensive, preoperative education for the patient, and 3) a team experienced in bariatric laparoscopic surgery, and with experience on evaluating and managing obese patients.

- The different types of surgery (restrictive and bypass) have different and substantive long-term effects on eating (the most important of all activities of daily living)—thus the term "behavioral surgery". One type of surgery does not fit all.

- "Successful" surgery has more potential for achieving meaningful, durable weight loss. Failure after surgery has much graver consequences.

- Deficiencies of vitamins and minerals are among the most common and troublesome long term complications. Adequate supplementation and monitoring are required.

- A widely accepted indication is a body mass index (**BMI**) 40 and over, or 35 to 40 with obesity-related comorbidity. Patients should have seriously tried to lose weight by other means. (In fact, most patients seeking surgery have seriously tried to lose 5 to 7 times.) There are trends toward accepting patients with lower BMIs and with a wider age range.

- How much weight loss is “enough”? How is “enough” determined? Success is difficult to determine. Rather than focusing on weight loss as the primary outcome measure, it is more appropriate to evaluate improvements in comorbidities and quality of life.

- Although it can be potentially life-extending treatment, most patients and doctors reject surgical intervention. No national health service can afford this surgery on a large scale.

BMJ October 28, 2006; 333: 900-03 Review article “ABC of Obesity” by John G Kral American Society for Bariatric Surgery

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***“MIRACULOUS”***

**10-3 A VERY EFFECTIVE TREATMENT FOR NEOVASCULAR MACULAR DEGENERATION**

Age-related macular degeneration (MD) is now epidemic, in conjunction with the rise in life expectancy. Roughly one in 3 persons will have MD by the age 75,

Actually, MD is a complex disorder which begins decades before a patient becomes symptomatic. In about 10% of patients with the condition, a derangement of vasculature beneath Bruch’s membrane leads to a new growth of blood vessels from the capillaries beneath the membrane into the subretina. This neovascular complication damages the retina. It is responsible for the vast majority of cases of legal blindness attributable to this disease.

In the 1970s, it was speculated that the growth of cancer cells depends on blood-vessel growth, and that control of vascular growth might prove to be an effective cancer therapy. Later, vascular endothelial growth factor (VEGF; a protein) emerged as an important molecule in the angiogenic process. Several recombinant monoclonal antibodies (ranibizumab is the latest FDA approved drug) have been designed to inhibit action of this factor.

Two large randomized clinical trials are reported in this issue of NEJM[1,2] Patients receiving intra-*vitreous* injection of ranibizumab monthly over 2 years gained, on average, more than one line of visual acuity. Controls lost vision. Ranibizumab was much more effective than photodynamic therapy. Bacterial infection within the eye occurred in 1 of every 2000 injections.

The efficacy of this treatment has been termed “miraculous”.

NEJM October 5, 2006; 355: 1493-95 Essay by Edwin M Stone, University of Iowa Carver College of Medicine, Iowa City.

**1** “ Ranibizumab for Neovascular Age-Related Macular Degeneration” NEJM October 5, 2006; 355: 1419-31, Original investigation, first author Phillip J Rosenfeld, University of Miami Miller School of Medicine, FL

**2** “ Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration” NEJM October 5, 2006; 355: 1432-44 First author David M Brown, Methodist Hospital, Houston TX

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**10-4 RANIBIZUMAB, BEVACIZUMAB, AND TREATMENT OF MACULAR DEGENERATION—THE PRICE OF SIGHT**

Although the neovascular form of MD accounts for only about 10% of cases of MD, it is responsible for the vast majority of the associated vision loss.

The FDA has approved ranibi-zumab (*Lucentis*; Genentech) for the treatment of neovascular age-related macular degeneration. Ranibizumab is a fragment of a recombinant monoclonal antibody that binds to, and inhibits, vascular endothelial growth factors in and beneath the retina. It is injected into the *vitreous* monthly. Treatment is likely to be required indefinitely.

It is a substantial advance which prevents vision loss and improves visual acuity. There are few side effects.

It is expensive – about $2000 for a single dose.

A precursor recombinant antibody, bevaci-zumab (*Avastin*), given intravenously, has been approved for treatment of metastatic cancer of the colon and rectum. It is now being given intravitreously (off label) in smaller doses at a much lower cost. It has not yet been directly compared with ranibizumab. The benefit/harm ratio compared with ranibizumab is not known. The cost differential is important.

NEJM October 5, 2006; 355: 1409-12 "Perspective", by Robert Steinbrook, national correspondent for the NEJM

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***This May Save The Patient Hours Of Pain.***

**10-5 DO OPIATES AFFECT THE CLINICAL EVALUATION OF PATIENTS WITH ACUTE ABDOMINAL PAIN?**

Abdominal pain is a common reason for emergency department visits. Of these, abut 45% are eventually diagnosed with non-specific pain; up to 30% have conditions requiring surgery—principally appendicitis , intestinal obstruction, and cholecystitis.

Clinicians have traditionally withheld opiate analgesia from patients with acute abdominal pain until after evaluation by a surgeon. This is out of concern that analgesia may alter the physical findings, and interfere with diagnosis. Older textbooks of surgery historically discouraged opiate analgesia for patients with acute abdominal pain. This rule has been firmly ingrained in the minds of physicians. However, the use of analgesia in emergency departments has increased in recent years.

This systematic search of the literature determined the impact of opiates on the rational clinical examination and operative decisions in patients with acute abdominal pain.

Conclusion: Opiate analgesia may alter the physical examination, but these changes do not result in significant increase in management errors.

STUDY

1. Reviewed 12 placebo-controlled randomized trials of opioid analgesia (3 in children and 9 in adults).

All reported changes in the history, physical examination, or diagnostic errors resulting in "management errors" due to opiate administration. Management errors were defined as performance of unnecessary surgery, or failure to perform necessary surgery in a timely fashion.

RESULTS

1. Changes in physical examination:
    1) Studies showed trends toward increased risks of altered findings on the abdominal examination due to opiate administration. Relative risk (**RR**) of altered findings (opiates vs placebo) = 1.51. (95% confidence interval (CI) = +0.85 to +2.69)
    2) When the analysis was restricted to 8 trials that reported significantly greater analgesia from the opiate, the RR = 2.13 (95% CI = +1.14 to +3.98).
    3) These trials exhibited significant heterogeneity.
2. Management errors as a marker for important changes in the physical examination:
    1) Opiates had no significant association with management errors. (RR = +0.3% absolute increase; CI = - 4.1% to + 4.7%). "The magnitude of this nonsignificant increase in incorrect decisions is very small. If it had been significant, 333 patients would need to receive opiates to result in one management error attributed to the analgesia." "These data are also compatible with fewer management errors among patients receiving opiates."
3. The evidence suggests that administration of opiates does not substantially alter the history of the illness.

DISCUSSION

1. While opiates might alter the physical examination in patients with abdominal pain, opiate administration seems to have negligible impact on clinical management.
3. None of the patients defined as having experienced a management error experienced significant morbidity or mortality.
4. We do not know whether analgesic doses of opiates cloud a patient's memory or instead calm the patient so he or she can provide a more coherent and accurate history.
5. Use of abdominal imaging may have decreased the emphasis on the physical examination as a decision-making tool in patients with acute abdominal pain. The results of this study primarily pertain to patients in whom the initial clinical examination does not yield a specific diagnosis.
6. "Given the humane duty of physicians to relieve pain and the totality of the available evidence, clinicians should administer analgesia unless further studies document adverse events in patients directly attributable to opiates."

CONCLUSION

Opiate administration may alter the physical examination findings, but these changes result in no significant increase in management errors.

JAMA October 11, 2006; 296: 1764-74 Original investigation, first author Sumant R Ranji, University of California, San Francisco.

The investigators provide a reminder of the pathogenesis of abdominal pain based on embryological development:

During embryogenesis, the afferent nerve roots travel with the arterial blood flow to the 3 visceral segments of the primitive embryo gut: foregut (stomach and proximal small intestine), midgut (distal small intestine, ascending and proximal transverse colon) , and hindgut (distal transverse colon and descending colon). Pain arising from the foregut localizes to the epigastrium; pain from the midgut localizes to the periumbilical region; pain from the hind gut localizes to the suprapubic and left lower quadrant area.

Visceral pain is elicited primarily by inflammation or ischemia stimulating the receptor neurons. Pain transmission is initially mediated by unmyelinated afferent fibers located on the walls of hollow viscera and capsules of solid organs. It is perceived as deep, diffuse pain. At the onset of an illness involving the viscera, the patient experiences pain that is difficult to describe or localize precisely. The pain is often midline. As the illness progresses, the peritoneum becomes affected. The peritoneum is richly innervated with large myelinated fibers which transmit the sensation of pain which is sharper and more easily localized. Clinical maneuvers which stretch the peritoneum elicit "peritoneal signs".

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***"The Ferritin Assay Provides A Simple Method Of Discriminating Between Iron Deficiency And Anemia Of Chronic Inflammation"***

**10-6 INVESTIGATING IRON STATUS IN MICROCYTIC ANEMIA**

- The investigation of possible iron deficiency has changed in recent years. Traditionally, measurements of iron and iron binding capacity were performed by laboratories. Serum ferritin[1] has become established as a more reliable test. To diagnose iron deficiency, measurement of ferritin is superior to iron and iron binding capacity or transferrin saturation.
- The ferritin assay provides a simple method of discriminating between iron deficiency and anemia of chronic infection. Serum ferritin less than 15 ug/L in adults confirms the diagnosis of iron deficiency. Levels over 100 ug/L rule it out. However, the probability of iron deficiency remains high until the ferritin level is greater than 40 ug/L for the general population, and greater than 70 ug/L or those with chronic inflammation or liver disease.
- Pretest probability of iron deficiency varies between patient groups. In elderly patients there is increasing probability of coexistent disease. This argues in favor of ferritin confirmation. Only about 1/3 of anemic patients over age 65 are iron deficient. The differential diagnosis includes: anemia of chronic inflammation; myelodysplastic syndrome; and other underlying bone marrow malignancies that are not usually seen in younger persons.
- Only about ½ of elderly patients with mean cell volume (**MCV**) less than 85 fL, and ¾ of the elderly with MCV less than 75 fL will have iron deficiency. About 20% of elderly patients with a MCV of under 75 fL will *not* have iron deficiency. The remainder (low cell volume *not* iron deficient) most likely will have the anemia of chronic inflammation. "Microcytic anemia alone is not sufficient to diagnose iron deficiency."

- In elderly patients with microcytic anemia a diagnostic trial of response to iron would not be appropriate without ruling out malignancy and other causes. Elderly patients with anemia require a ferritin assay in order to establish whether iron deficiency is present.
- In populations in which the prevalence of hemoglobiopathy genes is low, a finding of microcytic anemia is considered by some to be sufficient to indicate iron deficiency. However, this can lead to an erroneous diagnosis.
- For young women with heavy menses who have microcytic anemia, the pretest probability of iron deficiency may be sufficiently high that a ferritin assay is not required.
- In anemic patients, the probability of iron deficiency increases with decreasing MCV, but no specific cut-off value can be used. In patients with MVC greater than 95, the probability of iron deficiency is low.
- Once diagnosed, the cause of iron deficiency requires investigation.
- Response to iron therapy should be checked in several weeks. And with a further check at 2 to 4 months to ensure that hemoglobin has returned to normal. A 1 to 2 gm/dL rise confirms iron deficiency.

BMJ October 14, 2006; 333: 791-93 "Practice" Cases in Primary Care Laboratory Medicine, fist author Michael A Galloway, Sunderland Royal Hospital, UK

**1** Ferritin is an iron-protein (apoferritin) complex. It regulates iron storage and transport.

SI units normal range:

Ferritin Male 30 to 300 ug/L Female 10 to 200 ug /L

MCV 80 to 100 fL

*NEJM October 2004 351: 1550*

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***Is A Glass Of Wine With Dinner Part Of A Healthy Lifestyle?***

**10-7 ALCOHOL CONSUMPTION AND RISK FOR CORONARY HEART DISEASE IN MEN WITH HEALTHY LIFESTYLES.**

In prospective cohort studies, moderate alcohol consumption is consistently associated with lower risk of myocardial infarction (**MI**) than in persons who abstain.. Much of the benefit has been attributed to a higher HDL-cholesterol in drinkers.

Because of the risks associated with high alcohol intake, clinical guidelines do not recommend alcohol consumption. We have other safer and proven interventions to lower risk of cardiovascular disease. However, healthy behaviors are not mutually exclusive. Pursuit of exercise does not obviate the need for a healthy diet and smoking cessation.

This study considered the effect of long-term moderate alcohol consumption on incidence of MI in men who consistently reported healthy lifestyles. (Ie, alcohol in addition to the healthy lifestyle.)

Conclusion: In men already at low risk of MI, moderate alcohol intake was associated with a lowering of risk for MI.

STUDY

1. Over 51 000 men in the Health Professionals Follow-up Study (mean age 57) reported diet and other lifestyle factors in biennial questionnaires since 1986.
2. From this cohort, over 8800 men who were free of major illness participated in a prospective study. All reported 4 healthy lifestyle behaviors: 1) body mass index less than 25, 2) moderate to vigorous activity for 30 minutes or more daily, 3) not smoking, and 4) a high intake of vegetables, fruits, cereal fiber, fish, chicken, nuts, soy, and polyunsaturated fat. And, low consumption of trans fat, and red and processed meats.
3. Over 16 years of follow-up, determined incidence of non-fatal MI, and fatal coronary heart disease according to reported average daily intake of beer, wine, and liquor. The cohort was divided into quintiles according alcohol intake (g per day): 0; 0.1 to 4.9; 5.0 to 14.9; 15 to 29.0; and 30 and over.

RESULTS

1. During follow-up, 106 cases of MI were documented.
2. Hazard ratios for MI (multivariate adjusted) of average daily intake of alcohol compared with abstention:

| 0 | 0.1 to 4.9 | 5.0 to 14.9 | 15 to 29.0 | 30 and over. |
|---|---|---|---|---|
| 1.00 | 0.92 | 0.52 | 0.32 | 0.70 |

   (In absolute numbers, the differences between groups were small.)
3. "Our results were also qualitatively similar when we incorporated drinking frequency rather than average alcohol intake." For example, the hazard ratios in men who drank at least 3 days per week were 0.58 for risk of MI, and 0.52 for the combined endpoint of MI or revascularization."
4. Of the healthy lifestyles, abstinence from smoking (as compared with the other aspects of a healthy lifestyle) was associated with the lowest risk.

DISCUSSION

1. In this prospective analysis of men with healthy lifestyles, moderate alcohol consumption was associated with a lower risk for MI, with the lowest risk in men who drank an average of 5 to 30 g/d—approximately one half to 2 drinks. (No comment on any differences in outcome between types of drinks. No note on other cardiovascular outcomes. )
2. "While observational results such as these cannot prove causality, it seems unlikely, but not impossible, that an unknown confounding factor is sufficiently strongly associated with both alcohol use and risk for MI to have produced these findings."
3. Moderate alcohol consumption has been associated with lower risk of MI or death in population-based studies of subjects at higher risk for CHD, and in patients with known CHD.
4. The absolute benefit attributable to moderate intakes of alcohol is low in populations with healthy lifestyles
5. Even moderate drinking has potential health risks of breast cancer and acceleration of cirrhosis in patients with hepatitis C.
6. The individual and societal complications of heavy drinking are well known. "It is easy to understand

why clinical guidelines encourage physicians and patients to concentrate on seemingly more innocuous interventions."

7. "Our results suggest that moderate drinking could be viewed as a complement, rather than an alternative, to other lifestyle interventions."

CONCLUSION

In men with healthy lifestyles (not overweight, physically active, nonsmoking, and with a favorable diet), already at low risk for MI, moderate alcohol intake (approximately one half to 2 drinks per day) was associated with lower risk for MI.

Archives Int Med October 23, 2006; 1666: 2145-50 Original investigation, first author Kenneth J Mukamal, Beth Israel Deaconess Medical Center, Boston Mass.

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***"A Limited, but Sometimes Necessary Role"***

**10-8 EFFECTIVENESS OF ATYPICAL ANTIPSYCHOTIC DRUGS IN PATIENTS WITH ALZHEIMER'S DISEASE**

Psychotic symptoms affect more than half of patients with Alzheimer's disease (**AD**).

Second generation (atypical) antipsychotic drugs (**APD**) are widely used to treat AD patients. They have been considered to be at least as effective as conventional antipsychotic drugs such as haloperidol, and to have a lower risk of adverse effects. Their benefits are uncertain. Concerns about safety have emerged.

This study assessed the clinical effectiveness of APDs in patients with AD who had delusions, hallucinations, aggression, or agitation.

Conclusion: Although the atypical antipsychotic drugs were more efficacious than placebo, adverse effects limited their overall effectiveness.

STUDY

1. Multicenter, double-blind, placebo-controlled trial followed over 400 patients (mean age 78) with AD, or probable AD according to DSM-4. All were ambulatory and living at home or in an assisted-living facility.
2. All had delusions, hallucinations, aggression, or agitation which developed after the onset of dementia. Symptoms had to have occurred nearly daily during the previous week, or at least intermittently for 4 weeks. Symptoms were severe enough to disrupt functioning, and, in the opinion of study physicians to justify treatment with antipsychotic drugs. The level of psychopathology was moderate to severe, similar to that in studies of patients in nursing homes.
2. None had treatment with an anticholinesterase inhibitor or antidepressant.
3. Scores on Mini-mental State Examination (MMSE) varied from 5 to 26 (mean = 15) on a scale of 0 to 30.
4. Randomized to: 1) olanzapine (*Zyprexa*); 2) risperidone (*Risperidal*), 3) quetiapine (*Seroquel*), or 4) placebo. (*I omitted the data on quetiapine. It was not as effective. RTJ*)

5. Doses were adjusted as needed.
6. Primary outcomes = time to discontinuation of treatment for any reason. This integrated the judgments of patients, caregivers, and clinicians regarding efficacy, safety, and tolerability into a global measure of effectiveness that reflected therapeutic benefits in relation to undesirable effects.
7. Secondary outcome = attainment of minimal or greater improvement on the Clinical Global Impression of Change (**CGIC**) scale at 12 weeks.
8. Follow-up for up to 36 weeks.

RESULTS

1. Eighty two % of patients discontinued the initially assigned medication during the 36-week follow-up. *(Note that 18% continued.)*
2. The time (median in weeks) to discontinuation of treatment for any reason:

    Olanzapine 8
    Risperidone 7
    Placebo 8

    (Not statistically significant)
3. Time (median in weeks) to discontinuation because of lack of efficacy:

    Olanzapine 22
    Risperidone 27
    Placebo 9

    (Statistically significant favoring olanzapine and risperidone)
4. Discontinued assigned treatment due to intolerability:

    Olanzapine 24%
    Risperidone 18%
    Placebo 8%

    (Statistically significant)
5. Improvement in CGIC scale:

    Olanzapine 32%
    Risperidone 29%
    Placebo 21%
    (No statistically significant differences)
6. Adverse effects:

    A. Parkinsonism of extrapyramidal signs: olanzapine 12%; risperidone 12%; placebo 1%.

    B. Sedation: More common in the active drugs (15% to 24%); placebo (5%)

DISCUSSION

1. The median time to discontinuation for any reason (the primary outcome) ranged from 5 to 8 weeks, with

no significant difference among the 4 groups. Overall, the rates of discontinuation of treatment ranged from 77% to 85%. This is consistent with the opinions of expert clinicians who have recommended discontinuing or switching antipsychosis treatment after 2 to 4 weeks in patients who are not benefited.

2. The time to discontinuation of treatment due to lack of efficacy favored olanzapine and risperidone, but was offset by the increased rates of discontinuation of these drugs due to adverse effects.
3. Although the atypical antipsychotic drugs were more efficacious than placebo, adverse effects limited their overall effectiveness. Use may be restricted to patients who have few or no side effects and for whom benefits can be discerned.

CONCLUSION

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with AD.

NEJM October 12, 2006; 355: 1525-38 Original investigation by the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study, first author Lon S Schneider, University of Southern California, Los Angeles

Trial funded by the National Institutes of Health.

This pragmatic trial reflects the process used in clinical care.

Note that the authors do *not* state that these drugs should not be used, only that they may not benefit and may be associated with adverse effects which precludes their continuation.

An editorial in this issue of NEJM (pp 1604-06) by Jason Karlwish, University of Pennsylvania comments:

The FDA labels for antipsychotic medications state bluntly that they are not approved for treatment of dementia-related psychosis. They display a "black box" warning—"Elderly patients with dementia-related psychosis are at increased risk of death compared with placebo."

"Yet clinicians, including myself, continue to prescribe these drugs."

Both olanzapine and risperidone were equally effective and were superior to placebo in treating behavioral problems.

The benefit was limited to a subgroup of patients who either tolerated the drugs, or did not have side effects such as parkinsonism and sedation which limited duration of treatment.

These results, and the evidence that behavioral problems in AD can be reduced by specialized care (which stresses non-pharmacological management), suggest that these drugs have a limited, but sometimes necessary role in the care of patients with AD. They are perhaps best prescribed in systems of care that can provide the skills and expertise needed to ensure that the risks associated with the drugs are justified by their potential benefits.

The primary endpoint in the trial is an accurate reflection of a clinical event—the decision to change treatment because of the patient's condition is worsening or not improving sufficiently.

Flexible dosing (as used in this study) ensures one of the core principles of geriatric pharmacology "Start low and go slow, but go". Clinicians should start a drug at a dose at the lower end of the plausible therapeutic index and then increase the dose until there is efficacy or intolerable side effects *(I believe this applies to almost all drugs used long-term. RTJ)*

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***Should Primary Care Clinicians Advise Screening For Their High-risk Patients?***

**10-9 SURVIVAL OF PATIENTS WITH STAGE I LUNG CANCER DETECTED ON CT SCREENING**

In 1993, an early cancer detection project initiated a study of the early diagnosis of lung cancer (**LC**) in cigarette smokers by annual screening with spiral CT. More than 80% of LCs detected were stage I.

This is an update to 2005.

Does early detection followed by surgery produce benefits which justify screening?

Conclusion: Annual spiral CT can detect LC that is curable.

STUDY

1. Screened over 31 000 asymptomatic persons (age 40 to 86) at risk of LC—the great majority because of a long smoking history (median 30 pack-years).
2. The cohort was divided into 1) outcomes of the first (baseline) screen, and 2) outcomes of annual screens following the baseline screen.
3. Baseline screening group (n = over 31 000)
   A. A positive result was defined as the identification of at least one solid non-calcified pulmonary nodule 5 mm or more in diameter, or a non-solid, non-calcified nodule 8 mm or more in diameter.
   B. If such a nodule was found, the subject entered a protocol attempting to determine if the nodule was LC. The protocol included repeat CT at 3 months to gauge growth. If growth occurred, biopsy was performed. If no growth was observed the subject was referred for annual CT screening.
   C. Those with negative results were referred for annual CT screening.
4. Annual screenings (n = over 27 000)
   A. CT was considered positive if any newly identified non-calcified nodule was present, regardless of size. For those with nodules more than 3.0 mm in diameter, but less than 5 mm, CT was repeated in 3 to 6 months. If no growth, annual screening was continued.
   B. If a new non-calcified nodule over 5mm was detected, repeat CT was performed in 1 month. If growth occurred, a biopsy was made. If no growth, annual screening was resumed.
   *(Note: The protocol was somewhat more detailed than I reported. For details see pages 1764-65 RTJ)*
5. Determined number of LCs diagnosed.
6. The authors estimated 10-year LC-specific survival rates among subjects detected by biopsy with stage I LC (no nodes; no metastases) regardless of treatment received. Also determined outcomes for subjects who underwent surgical resection within one month.

RESULTS

1. Baseline cohort: (n = 31 567)
   Median age = 61; median pack years = 30
   Positive CT scan in 4186 (13%)
   Diagnosed as having LC = 405; 9.6% of the 4186 positive on CT; 1.3% of the entire cohort of 31 567.
2. Annual follow-up cohort: (n = 27 456)

Median age = 62; median pack years = 35

Positive CT scan in 1460 (5%)

Diagnosed as having LC = 74; 5% of the 1460 positive on CT; 0.3% of the entire cohort of 27 456..

3. Overall, 484 were diagnosed as LC. 412 (85%) had stage I; 302 underwent resection within one month
4. Estimated 10-year LC-specific-survival rate = 88% for all those with stage I regardless of treatment given. Of those undergoing resection within 1 month, 10-year LC-specific-survival rate = 92%. [Difference = 4%; NNT to benefit one = 25]
5. Eight participants with stage I who did not receive treatment died within 5 years.
6. Operative mortality = 0.5% (one in 200).

DISCUSSION

1. Stage I LC is the only stage at which cure by surgery is highly likely.
2. CT scanning by the study protocol can detect clinical stage I LC in a high proportion of persons when it is curable by surgery. "In a population at high risk for lung cancer, such screening could prevent some 80% of deaths from lung cancer."
3. Are the results sufficiently effective to justify screening persons at high risk? For patients age 40 and older at high risk, baseline screening led to detection of LC in 1.3%. Annual screens led to detection in 0.3%. (This is actually a more favorable rate of detection of breast cancer by mammography (0.6% to 1% on baseline screen)
4. The authors consider screening and appropriate surgery to be cost effective, similar to the cost effectiveness of mammography.

CONCLUSION

Annual spiral CT screening for persons at high risk of LC because of smoking can detect LC that is curable.

NEJM October 26, 2006; 355: 71 Original multicenter investigation by the International Early Lung Cancer Action Program Investigators. (I-ELCAP) First author Claudia I Henschke, Weill Medical College of Cornell University, New York

Comments by the editor of *Practical Pointers*:

I congratulate the investigators for their dedication to this project over many years.

What is the benefit / harm-cost ratio of this intervention?

Benefits:

It seems reasonable to assume that, if a solitary, localized LC is removed completely, the patient is "cured" and will not succumb to LC—provided it does not recur. There is no way to determine which individual patient will be cured.

Many patients will be elderly. (Most subjects in this trial who underwent screening and surgery were over age 60; many over age 70 and 80). Their remaining years of quality life are limited under any circumstances. They may succumb to co-morbid conditions.

Some will not cease smoking. Long-term benefits of screening will be considerably diluted if the patient continues to smoke. (The investigators did not address this point.)

Harms:

1) Anxiety, interruption of daily activities, and bother. Note that over 31 000 persons were screened; over 27 000 had repeated screens; 4000 patients had a suspicious nodule and were entered into the protocol.
2) Radiation injury: I do not believe that the radiation dose of repeated CT is harmless. Adverse outcomes may appear decades later.
3) Operative mortality = 0.5% (one in 200).

Cost:

The authors state screening is cost-effective. When a patients with a positive screen enters the protocol, expenses will continue to mount. If screening were to be applied to all long-term smokers in the country, costs would be enormous. I believe health-care funds would be more efficiently directed elsewhere.

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**10-10 ORAL RENIN INHIBITORS**

Inhibition of the renin-angiotensin system[1] is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders.

The idea of blocking the *action* of renin on angiotensinogen (thus reducing levels of angiotensin I and angiotensin II) has existed for many years. Active research to produce an effective oral renin inhibitor has been conducted ever since.

Clinical development of oral renin inhibitors has been far more challenging than originally expected. Bioavailability has been low due to poor gastrointestinal absorption and there has been substantial first-pass metabolism, short duration of action, and weak BP-lowering activity.

Pharmaceutical companies, despite encountering many difficulties, are continuing their attempts to develop effective orally administered renin inhibitors. Several, termed “kirins” have been studied. Aliskirin (a non-peptide) is the only one that has progressed to phase-III clinical trials. In healthy volunteers, plasma concentrations are dose-dependent; and plasma half-life averages 24 hours, making it suitable for once-daily administration. The unmetabolized drug is excreted almost entirely by the biliary tract. Given to normal volunteers, aliskirin produces a dose-dependent reduction in plasma renin *activity* thus lowering plasma concentrations of angiotensin I and angiotensin II, and urinary aldosterone. At the same time plasma renin levels rise.[2]

Alsikirin phase II clinical trials in hypertensive patients:

One trial enrolled patients with mild to moderate hypertension comparing losartin (an angiotensin II blocker) with aliskirin. The reduction in the daytime systolic BP were similar (8 to 11 mm Hg). The lowering persisted for 24 hours with similar BP levels during nighttime between the 2 drugs. With aliskirin, plasma renin *activity* fell by 50 to 80%. Renin *activity* doubled with losartin.

A second trial randomized hypertensive patients to aliskirin, irbesartan ( an angiotensin II blocker), or placebo. The lowering of diastolic BP was greater in the aliskirin group. The frequency of adverse effects was similar between aliskirin and placebo with the exception of diarrhea, which was more frequent with aliskirin.

Compared with ACE inhibitors, renin inhibitors have fewer side-effects.

Novartis is now conducting phase III trials to measure effects of aliskirin on left ventricular hypertrophy in patients with hypertension. Further trials are concerned with effects on heart failure, and reduction in urinary albumin to creatinine ratio.

However, to establish a new drug class as a valuable addition to available therapeutic options requires proof of beneficial effects on morbidity and mortality. This challenge might take another 7 to 8 years.

Renin inhibitors might offer additional safety for patients with cardiovascular disease and concomitant renal disease because they are preferentially eliminated via the liver.

Renin inhibitors might be useful when combined with other antihypertension drugs.

Lancet October 21, 2006; 368: 1449-56 Review article, first author Jon A Staessen, University of Leuven, Belgium.

**1** Traditionally, the system has been termed the "renin-angiotensin system". I believe, for consistency and clarity, the system should be termed the "angiotensinogen-angiotensin I-angiotensin II-aldosterone" (A-AI-AII-A) system. This describes the active physiological mediators. Renin, and the angiotensin-converting enzyme facilitate the conversion from one step to another. (The enzyme renin aids the conversion of angiotensinogen to angiotensin I; the angiotensin-converting enzyme aids conversion of angiotensin I to angiotensin II.)

**2** This is a confusing point. A negative feedback mechanism exists between angiotensin II and renin production. Normally, as angiotensin II levels increase, renin *production* by the kidney decreases. When angiotensin II levels are lowered by the action of aliskirin, this restraining activity is lost, and *production* of renin by the kidney increases. Blood levels of renin rise dramatically. Nevertheless, the aliskirin *action* on the excess renin continues, and angiotensin I and angiotensin I levels continue to be low.

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## 10-11 THE ANGIOTENSINOGEN-ANGIOTENSIN I - ANGIOTENSIN II- ALDOSTERONE SYSTEM

***Also Known As the Renin-Angiotensin System***

The angiotensinogen-angiotensin I-angiotensin II-aldosterone system (**A-AI-AII-A**) is a basic physiological system which helps maintain homeostasis. The complexity of the system is maddening. *(I prepared this simplified abstract for my own edification and enjoyment. RTJ)*

Inhibition of the system has been termed one of the most effective and important ways to intervene in the pathogenesis of cardiovascular and renal disorders including hypertension, left ventricular systolic dysfunction, acute myocardial infarction, chronic renal disease (eg, diabetic). It also reduces risk when given to patients at high risk for cardiovascular disease.

The system:

1. Angiotensinogen: A glycoprotein synthesized and continuously secreted, principally by the liver. Acts as

a substrate for renin. Renin cleaves a 10-amino acid from angiotensinogen to form angiotensin I. Changes in the level of angiotensinogen can influence production of angiotensin I and II synthesis, and influence BP. Circulating levels of angiotensinogen are increased by estrogens, and rise during pregnancy and with administration of birth control pills. Hypertension may result. Increased levels have been associated with essential hypertension.

2. Angiotensin I:

A decapeptide cleaved from angiotensinogen by renin. It is present in many vascular beds. Its only function is to act as a precursor of angiotensin II. It is rapidly converted into angiotensin II by the angiotensin-converting enzyme

3. Angiotensin II

A. Is produced by action of angiotensin converting enzyme (ACE) on angiotensin I. Conversion is very rapid. Much of this takes place on or within the surface of vascular beds. Angiotensin II acts via diverse coordinated mechanisms to preserve blood volume and regulate arterial BP which it maintains in the face of hypotensive challenges.

B. It is a potent vasoconstrictor. Given intravenously, it acts immediately to increase total peripheral resistance and raise arterial BP. It also increases sympathetic neurotransmission, and cellular growth.

C. It acts directly on the kidney to inhibit excretion of sodium and water and increase excretion of potassium. Regulation of sodium excretion is an important means of maintaining blood volume and controlling BP in the face of large swings in sodium intake.

D. It also acts directly on the adrenal cortex to increase adrenal aldosterone secretion, and thereby influences sodium retention and potassium excretion by the kidney.

4. Aldosterone: (The sodium retaining; potassium excreting hormone)

A. Is a mineralocorticoid" (electrolyte-balancing) steroid, produced and secreted by the adrenal cortex, under the influence of angiotensin II; and in response to low sodium levels and low blood volume.

B. It action on the kidney increases resorption of sodium and water and preserves blood volume and BP. It increases excretion of potassium.

C. In states of excess, it leads to hypertension.

Enzymatic steps in the A-AI-AII-A system

1. Renin:

An enzyme (a glycoprotein protease) produced by the juxtaglomerular apparatus of the kidney.

It controls the first, rate-limiting step in the system by cleaving angiotensinogen to form angiotensin I and thus determines formation of angiotensin II.

Renin is produced, stored, and secreted by the juxtaglomerular cells in the kidney. It is taken up by arterial walls and acts locally to degrade angiotensinogen to angiotensin I.

Secretion is controlled by several mechanisms:

A. NaCl concentrations in the distal ascending tubule of the kidney:

1) Decreasing concentrations in the tubule (NaCl depletion) causes increased secretion.

2) Increasing concentrations (NaCl excess) causes decreased secretion.

B. Baroreceptors in the afferent arteriole of the glomerulus sense blood pressure:

1) Decreased pressure (tension) increases secretion.

2) Increased pressure reduces secretion.

C. Circulating norepinephrine also activates the juxtaglomerular apparatus and increases secretion.

D. There is a normal negative feedback mechanism between angiotensin II levels and renin secretion. (As noted in the preceding article). Decreasing activity of angiotensin II (as produced by renin inhibitors, ACE inhibitors, and angiotensin II blockers) will increase renin output.

Drugs which block the A-AI-AII-A system (one potential and four widely applicable):

1. Beta blockers inhibit release of renin from the kidney.
2. Renin inhibitors (as noted in the preceding article).
3. ACE inhibitors (The "pril" drugs: eg captopril)
4. Angiotensin II blockers (The "sartan" drugs: eg losartan)
5. Aldosterone blocker (spirinolactone).

Review prepared by the editor of *Practical Pointers*. Much of the data was obtained from Goodman and Gilman *The Pharmacological Basis of Therapeutics* 10th edition (2001)

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