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HIGHLIGHTS SEPTEMBER 2000

9-1 EFFICACY OF SELECTIVE SEROTONIN-REUPTAKE INHIBITORS IN PREMENSTRUAL SYNDROME

SSRIs are safe and effective first-line therapy for severe PMS.

9-2 RECOGNITION OF PREMENSTRUAL DYSPHORIC DISORDER AND ITS TREATMENT

Several features suggest that PMDD is distinct from other mood disorders. The dysphoria is cyclical, the physical symptoms unique (breast tenderness and bloating the most common) and tightly linked to phases of the cycle. There is a typical and predictable "on-offness". Symptoms disappear with the menopause and pregnancy. Suppression of the cyclicity of gonadal hormones can bring relief. Hormone replacement therapy can provoke recurrence of symptoms in women with a past history of PMDD.

9-3 IMPROVING THE CARE OF PATIENTS WITH GENITAL HERPES

Many cases of genital herpes **(GH)** remain unrecognized. Patients may have symptoms and signs unrecognized by either themselves or their clinicians. "Patients often present having had frequent painful attacks for many years." This despite the availability of effective antiviral drugs.

Patients often believe that they are infectious only during symptomatic episodes despite evidence that most transmission occurs from asymptomatic shedding of the virus.

9-4 TYPE OF ALCOHOL CONSUMED AND MORTALITY FROM ALL CAUSES, CORONARY HEART DISEASE, AND CANCER.

Wine intake may have a beneficial effect on all-cause mortality that is additive to that of alcohol. The effect is attributable to a reduction in death from coronary disease and cancer. Wine may contain one or several substances that add to the beneficial effect of intake of small amounts of alcohol.

9-5 SEVEN-YEAR CHANGES IN ALCOHOL CONSUMPTION AND SUBSEQUENT RISK OF CARDIOVASCULAR DISEASE IN MEN

Among men with initially low alcohol consumption (1 drink per week of less). a subsequent moderate increase in alcohol consumption may lower CVD risk.

"Given the potential risks and benefits associated with alcohol consumption, physicians counseling of patients must be individualized in the content of primary prevention."

9-6 AGE OF DRINKING ONSET AND UNINTENTIONAL INJURY INVOLVEMENT AFTER DRINKING

Drinking onset at ages younger than 21 years was associated with experiencing more alcohol-related injuries later in life. Our young patients who begin smoking and drinking are calling out for help. We must heed their cry.

9-7 CHANGES IN DIET, WEIGHT, AND SERUM LIPID LEVELS ASSOCIATES WITH OLESTRA CONSUMPTION.

Consumption of olestra, a new fat substitute, was associated with benefits on lipid profiles and a reduction in total fat intake. Changes in LDL- and HDL-cholesterol were clinically significant. RTJ

9-8 WHOLE GRAIN CONSUMPTION AND RISK OF ISCHEMIC STROKE IN WOMEN.

Higher intake of whole grain foods was associated with a lower risk of ischemic stroke independent of known risk factors for CVD.

9-9 HIGH BLOOD PRESSURE AND DIABETES MELLITUS

Intensive control of BP in patients with combined diabetes-hypertension to levels below 135/85 reduces risk of cardiovascular events. All 4 drug classes — diuretics, beta-blockers, ACE inhibitors, and calcium blockers — are effective.

Most patients will require combined therapy to obtain BP goal of 130/85

9-10 OBESITY SURGERY — ANOTHER UNMET NEED

For patients with morbid obesity (BMI > 40; weight in kg / height in meters^2) a conservative approach to weight control is doomed to failure.

Good results have been obtained from surgery (banding gastroplasty; gastric bypass) in these patients. Comorbidity decreases as a result of even modest weight loss . The National Institute of Health in the United States has suggested that surgery is the most effective treatment for selected patients who are morbidly obese.

9-11 END-OF-LIFE CONVERSATIONS

"We conclude that end-of-life conversations must become a routine, structured intervention in health care, and that advanced care planning is best viewed as one component in a series of ongoing end-of-life discussions."

9-12 HORMONE REPLACEMENT THERAPY AND PERIPHERAL ARTERY DISEASE

In this population-based study, postmenopausal women who took HRT for a year or more had a decreased risk of PAD.

9-13 MULTIPLE COMPLEX CORONARY PLAQUES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Patients with acute MI may harbor multiple complex coronary plaques that are associated with adverse clinical outcomes. Plaque instability may occur as a widespread process throughout the coronary arteries.

Atherosclerosis is a widespread disease. Not only of the coronary arteries, but also of carotid, renal, peripheral arteries, and the aorta. When a coronary lesion is identified, we can be certain that lesions are present elsewhere in the arterial tree as well as elsewhere in the coronary tree. We are dealing with a wide-spread, not a localized disease. Medical therapy, not surgery, is the ultimate answer to primary prevention and treatment.

We now have excellent measures to prevent or delay the process. If these fail and individuals develop clinical disease, we still may have a good chance at stabilizing the disease with all-out medical therapy and life-style changes.

9-14 CURRENT ROLE OF PLATELET GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE CORONARY SYNDROMES

Intravenous GpIIb/IIIa inhibition therapy has greatly enriched the therapeutic armamentarium for patients with ACSs. Administered at the time of urgent angiography with PTCA, coronary revascularization, or empirically in the emergency department at presentation, these agents build on the antithrombotic template of aspirin and heparin.

GpIIb/IIIa inhibition merits a prominent role in the management of ACSs, either medically or in conjunction with PTCA.

9-15 THE ROLE OF THE INTERLEUKIN-1-RECEPTOR ANTAGONIST IN BLOCKING INFLAMMATION MEDIATED BY INTERLEUKIN-1

The increased production of the cytokine interleukin-1 during an inflammatory disease contributes to the pathologic process by binding to and triggering its receptor. Normally enough IL-1 receptor antagonist is produced to hold the interleukin-mediated inflammation at bay. In cases of runaway inflammation there is an insufficient amount of IL-1-receptor antagonist to control the activity of IL-1. Administration of exogenous IL-1RA should ameliorate inflammatory disease.

9-16 RISKS OF INTERRUPTING DRUG TREATMENT BEFORE SURGERY.

The problem of abrupt drug cessation is not sufficiently recognized. Drug information formularies should identify the best substitutes for drugs that cannot be given parenterally. Hospital pharmacists play an important role in providing guidance.

9-17 COMPARISON OF ST JOHN'S WORT AND IMIPRAMINE FOR TREATING DEPRESSION

This Hypericum extract was therapeutically equivalent to imipramine in treating mild to moderate depression. It was better tolerated than imipramine.

9-18 DIAGNOSIS AND TREATMENT OF CHRONIC ABACTERIAL PROSTATITIS:

A Systematic Review

No standard diagnostic tests. Treatment trials were weak. The routine use of antibiotics and alpha-blockers to treat chronic abacterial prostatitis is not supported by the existing evidence.

RECOMMENDED READING

9-11 END-OF-LIFE CONVERSATIONS

REFERENCE ARTICLES

9-3 IMPROVING THE CARE OF PATIENTS WITH GENITAL HERPES

9-14 CURRENT ROLE OF PLATELET GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE CORONARY SYNDROMES

9-15 THE ROLE OF THE INTERLEUKIN-1-RECEPTOR ANTAGONIST IN BLOCKING INFLAMMATION MEDIATED BY INTERLEUKIN-1

9-18 DIAGNOSIS AND TREATMENT OF CHRONIC ABACTERIAL PROSTATITIS:

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9-1 EFFICACY OF SELECTIVE SEROTONIN-REUPTAKE INHIBITORS IN PREMENSTRUAL SYNDROME

Premenstrual syndrome **(PMS)** consists of regularly recurring psychological or somatic symptoms, or both. The symptoms occur specifically during the luteal phase of the cycle and are relieved by the onset of, or during menstruation.

Mild symptoms occur in the majority of women of reproductive age and can be managed by conservative measures (exercise, dietary regulation, cognitive-behavioral therapy). For about 1 in 20 women, symptoms are severe enough to completely disrupt their lives. This is termed "premenstrual dysphoric disorder" **(PMDD).**

The causes of PMS are not clear. Many treatments have been suggested. The response to placebo treatment is substantial.

Currently, it is suggested that a differential sensitivity to circulating hormones, rather than abnormal concentrations causes PMS. There is increasing evidence that serotonin is important in pathogenesis. Selective serotonin-reuptake inhibitors **(SSRIs)** have been used as first-line therapy. Fluoxetine has been approved by the FDA for this purpose.

This meta-analysis assessed efficacy of SSRIs in treatment of PMS.

Conclusion: SSRIs are effective first-line therapy.

STUDY

1. Review included 15 randomized, placebo-controlled studies (over 900 women). Several different SSRIs were included — mainly fluoxetine (*Prozac; Sarafem*) and sertraline (*Zoloft*).
2. Calculated standardized differences between treatment and placebo to obtain an overall estimate of efficacy. Primary outcome = reduction in overall symptoms.

RESULTS

1. Overall standardized difference favored SSRIs. SSRIs were 7 times more likely to reduce symptoms than placebo. Both physical and behavioral symptoms improved. Fluoxetine was the most effective.
2. No significant difference in response between continuous and intermittent dosing.
3. Withdrawal due to adverse effects was over twice as likely in the treatment group.

DISCUSSION

1. Irritability is commonly cited as a major reason for seeking treatment. SSRIs had a significant positive effect on this symptom.
2. In PMS, unlike response of depression, SSRIs may become effective in a few days.
3. No difference between continuous and non-continuous (luteal-phase) dosing. Intermittent dosing is cheaper, and may reduce frequency of adverse effects and withdrawal.
4. Insomnia, gi disturbance, and fatigue were the most commonly reported adverse effects.
5. Recurrence rates of PMS after discontinuation of treatment are high. PMS can be expected to last until the menopause. Any intervention must be effective, safe for the long-term, and free of adverse effects. Long-term safety of SSRIs has been demonstrated by studies of affective disorders.

CONCLUSION

SSRIs are safe and effective first-line therapy for severe PMS.

Lancet September 30, 2000; 356: 1131-36 Meta-analysis, first author Paul W Dimmock, Keele University, Stoke-on-Trent, UK **www.thelancet.com**

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9-2 RECOGNITION OF PREMENSTRUAL DYSPHORIC DISORDER AND ITS TREATMENT

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

In patients with PMDD, SSRIs decrease emotional and physical symptoms and produce a moderate to marked improvement in up to 70% of patients. This compares with an improvement in 20% of those taking placebo, and 30% in those taking non-SSRI anti-depressants.

Several features suggest that PMDD is distinct from other mood disorders. The dysphoria is cyclical, the physical symptoms unique (breast tenderness and bloating the most common) and tightly linked to phases of the cycle. There is a typical and predictable "on-offness". Symptoms disappear with the menopause and pregnancy. Suppression of the cyclicity of gonadal hormones can bring relief. Hormone replacement therapy can provoke recurrence of symptoms in women with a past history of PMDD.

The function of the hypothalamic-pituitary-adrenal axis is normal in PMDD, unlike that in patients with major depression. Response to therapy is more rapid than in depressive disorders. Withdrawal results in rapid recurrence of symptoms. The most common adverse-effects are insomnia, gastrointestinal disturbance, and fatigue. Most adverse effects are associated with high doses.

Other treatments have reported improvement in PMDD — calcium carbonate and vitamin B6. They are not as effective as SSRIs.

All studies have excluded women under age 18. It is prudent to wait for further studies before prescribing SSRIs in young girls.

Lancet September 30, 2000; 356: 1126-27 Editorial by Meir Steiner, McMaster University, Hamilton, Ontario, Canada. **www.thelancet.com**

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REFERENCE ARTICLE

9-3 IMPROVING THE CARE OF PATIENTS WITH GENITAL HERPES

Many cases of genital herpes **(GH)** remain unrecognized. Patients may have symptoms and signs unrecognized by either themselves or their clinicians. "Patients often present having had frequent painful attacks for many years." This despite the availability of effective antiviral drugs.

Patients often believe that they are infectious only during symptomatic episodes despite evidence that most transmission occurs from asymptomatic shedding of the virus.

Herpes simplex is classified as type 1 and type 2. Type 1 causes herpes labialis. Most infected individuals remain asymptomatic. Type 2 is most acquired sexually, often by oral sex. Genital herpes can result from infection with either type. Now about half of episodes of genital herpes are attributable to type 1, although recurrences are far more likely after infection with type 2.

After initial infection, both viruses remain latent in the dorsal root ganglion, and are never cleared. Reactivation results in either symptomatic disease, or asymptomatic shedding. Initial infections may not cause symptoms, but are followed by seroconversion.

Viral culture is the diagnostic test of choice. It is relatively rapid, allows typing and is widely available.

Management:

First episode: Often presents with widespread anogenital ulceration and severe pain. All patients should receive an oral antiviral and supportive treatment. (Most patients with severe GH feel depressed and tearful.) All 3 available agents are effective. Choice is largely a matter of cost and patient acceptability. Treatment should be initiated when a clinical diagnosis is made. Swabs for confirmatory diagnosis should be obtained before starting antivirals. Oral antivirals are as effective as iv preparations. Topicals are of no value.

Recurrent GH:

Most are less severe than the first. Treatment options include bathing in saline, short courses of antivirals, and long-term suppressive therapy. Episodic treatment reduces symptoms by only 1 to 2 days, and needs to be started as soon as possible. Patients should maintain a supply of the drug at home.

Suppressive treatment is generally offered to those experiencing more than 6 recurrences a year. It can make a major difference in physical and psychological wellbeing A fixed term of suppression (eg, 1 year) should be agreed upon. Treatment should then be discontinued to assess the natural pattern of the disease. Frequency of attacks may naturally decrease over time.

All patients should receive counseling on prevention of transmission and implications of infection with HV during pregnancy.

Addressing Patient's Concerns.

How did I get this? How long have I had it? Has my partner been unfaithful? Is it incurable? Am I infectious?

It is helpful to discuss the possibility that infection can be present without recognizable signs in them or their partners. Infidelity is not necessarily implied. Transmission from asymptomatic individuals in monogamous relationships can occur after several years, causing severe psychological distress.

There is no evidence that the virus causes long-term sequelae such as cancer or infertility. The tendency is for attacks to decrease with time. Reassure that the virus is not transmitted by non-sexual contact. No special precautions need to be taken within the family except for the normal hygienic measures.

Genital Herpes In Pregnancy

The potential effects of GH in pregnancy need to be discussed. Around 85% of neonatal herpes results from perinatal transmission during vaginal delivery. Severe neurological impairment or death can result. Acyclovir has not been specifically licensed for use in pregnancy, but it has been used fairly extensively. A pregnancy registry of women receiving acyclovir showed no discernable pattern of defects in infants.

Acquisition of new GH in the third trimester of pregnancy can have serious implications for the neonate and requires specialist attention.

BMJ September 9, 2000;321: 619-23 "Clinical Review" first author Susan Drake, Heartlands Hospital, Birmingham UK **www.bmj.com/cgi/content/full/321/7261/619**

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9-4 TYPE OF ALCOHOL CONSUMED AND MORTALITY FROM ALL CAUSES, CORONARY HEART DISEASE, AND CANCER.

A J-shaped relationship between alcohol intake and mortality has been reported in many large cohort studies.

This study asks — What type of alcohol is most beneficial?

Conclusion: Wine

STUDY

1. Pooled cohort studies of over 13 000 men and over 11 000 women in which intakes of beer, wine, and spirits were noted.
2. Determined total number of deaths, deaths from coronary heart disease, and deaths from cancer during over 250 000 person-years of follow-up.

RESULTS

1. Over 4800 persons died.
2. J-shaped relations were found. (Ie, light-drinkers had less morbidity than abstainers; heavy drinkers, more morbidity.)
3. Compared with non-drinkers:
   A. Light drinkers who did not take wine had a relative risk of death from all causes of 0.9.
   B. Light drinkers who included wine had a relative risk of 0.66
   C. Heavy drinkers who avoided wine were at higher risk of death from all causes than heavy drinkers who included wine.
4. Wine drinkers had a significantly lower mortality from both coronary heart disease and cancer than did non-wine drinkers.

DISCUSSION

1. "In this prospective, population-based analysis, we found a significant decrease in all-cause mortality among wine drinkers compared with non-wine drinkers at all levels of alcohol intake."
2. "Cross-sectional comparisons at the population level have shown a strong inverse relation

between wine intake and incidence of coronary heart disease, but no such relation with other types of alcoholic beverages." (*See citations 7-10 p 418*)

3. "Wine drinkers may have had a small but regular intake compared with beer drinkers, whose drinking patterns may more closely resemble binge drinking; such a difference in drinking pattern could explain our findings."

CONCLUSION

Wine intake may have a beneficial effect on all-cause mortality that is additive to that of alcohol. The effect is attributable to a reduction in death from coronary disease and cancer. Wine may contain one or several substances that add to the beneficial effect of intake of small amounts of alcohol.

Annals Int Med September 19, 2000; 133: 411-19 Original investigation, first author Morten Gronbaek, University of Copenhagen, Denmark. **www.annals.org**

Comment:

The epidemiologic evidence of benefit from intakes of small amounts of alcohol is so persuasive that some authorities now include this factor in case-control studies comparing risk factors for coronary disease. A recent report from the Nurse's Health Study (*Practical Pointers July 2000; 7-3*) included a half a drink of alcoholic beverage daily (along with exercise and diet) as a benefit-factor. By implication, abstinence may be considered a risk-factor.

Even heavy drinkers who included wine had some protection as compared with heavy drinkers who did not take wine. The pattern of wine drinking (imbibing smaller amounts regularly with meals, rather than binge-drinking as with beer) may add to the benefit.

If it were not for the social and legal constraints associated with alcohol, and if the usual limits applied to prescription drugs were applied to alcohol, clinicians would routinely prescribe it for primary prevention as well as secondary prevention. Indeed, it might be one of the most frequently prescribed drugs.

The debate about benefits/harms of alcohol runs on. Is the protective effect due to alcohol itself, or to alcohol + some unknown factors in wine?

At any rate, the amount consumed to obtain benefit must be small. No more than 1 drink a day and most likely less. I believe the evidence of benefit tilts toward wine. RTJ

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9-5 SEVEN-YEAR CHANGES IN ALCOHOL CONSUMPTION AND SUBSEQUENT RISK OF CARDIOVASCULAR DISEASE IN MEN

Observational and experimental evidence strongly suggests that moderate alcohol consumption is related to a reduced risk of cardiovascular disease **(CVD).** Comparisons according to beverage type suggest that the alcohol, rather than the type of alcoholic beverage is responsible factor.

This study asked — if men change their alcohol consumption later in life, will this affect CVD risk? (A primary prevention study.)

Conclusion: Among men with initially low alcohol consumption (≤ 1 drink per week) a subsequent moderate increase in consumption was associated with a lower CVD risk.

STUDY

1. Prospectively followed over 18 000 men age 40 to 84 at baseline. None had a history of CVD or cancer.
2. Recorded alcohol consumption at baseline and after 7 years.
3. Subsequent to the 7-year questionnaire, participants were followed for an additional 6 years.

RESULTS

1. In general, this cohort of apparently healthy men consisted of light to moderate drinkers. About 20% were essentially abstainers. Abstention increased with increasing age. Mean consumption declined slightly with age. Only 1% reported a large increase.
2. At baseline 40% of men consumed 1 drink per week or less; 25% consumed 1 drink or more than one drink daily. Only about 3% drank 2 drinks or more daily.
3. Relative risk of CVD associated with initial weekly alcohol consumption:

< 1 drink/w	1 to < 2 drinks/w	2 to < 4/w	4 to < 7/w	1/d	2 or more/d
1.00	0.99	0.79	0.78	0.77	0.95

4. Effect of increasing intake:
   A. Among men initially consuming ≤ 1 drink per week, those with moderate increases in intake to between 1 and 6 drinks per week (n = 2000), had a borderline significant *decrease* of 29% in risk of CVD compared with men who did not change intake.
   B. Among men initially consuming 1 drink per day or more, those who increased intake had a 63% *increase* in CVD compared to men who did not change intake.

DISCUSSION

1. Over 7 years, among men who initially consumed one drink or less per week (including abstainers), a small increase in intake to 1 to 5 drinks per week was associated with a 29% reduced risk of subsequent CVD.

2. Men initially consuming 7 or more drinks per week had no further decline in CVD as a result of an increase in intake over the next 6 years.
3. Men who increased intake from 1 drink daily to 2 or more daily had a 63% *increased* risk.
4. Effects of changes in consumption were independent of other recognized risk factors for CVD.
5. Other epidemiologic studies have consistently reported J-shaped relationship between alcohol consumption and risk of CVD, with the lowest risk being at about 1 drink per day.

CONCLUSION

Among men with initially low alcohol consumption (1 drink per week or less). a subsequent moderate increase in alcohol consumption may lower CVD risk.

"Given the potential risks and benefits associated with alcohol consumption, physicians counseling of patients must be individualized in the content of primary prevention."

Archives Int Med September 25, 2000; 160: 2605-12 Original investigation based on the Physician's Health Study, first author Howard D. Sesso, Brigham and Women's Hospital, Boston Mass.
www.archintern.med.com

Comment

Is it possible that benefits on secondary prevention may be greater? RTJ

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9-6 AGE OF DRINKING ONSET AND UNINTENTIONAL INJURY INVOLVEMENT AFTER DRINKING

Thirty-one percent of persons who died as a result of non-traffic unintentional injuries in the US from 1973 to 1995 had blood alcohol levels of 0.10 or higher. In 1997 unintentional injury was the leading cause of death for persons age 1 to 34 years.

The age of drinking onset is strongly related to alcohol dependence. Persons who begin drinking before age 14 are at least 3-times more likely to experience alcohol dependence during their lifetime than those beginning after age 21.

Alcoholism is the leading risk factor for injury. Programs that systematically screen injured persons for alcoholism and offer them brief intervention and referral for treatment can markedly reduce injuries.

Nearly one third of persons injured under the influence of alcohol never in their life have met alcohol-dependence criteria.

This study asks: Is drinking onset at an early age an indicator of increased risk of alcohol-related injury later in life?

Conclusion: Early-age onset of drinking was associated with subsequent unintentional injury.

STUDY

1. The National Longitudinal Alcohol Epidemiology Survey (1992), a cross sectional survey of a representative sample of the US population, randomly selected over 42 000 adults.
2. Main outcome — unintentional injury involvement while under the influence of alcohol by age of drinking onset in the past.

RESULTS

1. Relative to respondents who began drinking at age over 21, those who started before age 14 were significantly more likely to have been injured while under the influence of alcohol.
2. Adjusted age-related odd ratios of younger persons (compared with beginning after age 21) experiencing subsequent unintentional injury when under the influence:

< age 14	age 14	age 19	age 20
2.98	2.96	1.42	1.39

DISCUSSION

1. Delaying the age persons begin drinking (such as setting the minimum legal drinking age to 21 years) reduces alcohol-dependence, alcohol-related traffic deaths, and deaths from unintentional injuries.
2. This study indicates that early age of onset of drinking is associated with frequent heavy drinking later in life, not only for persons with diagnosable alcohol dependence, but other drinkers as well.
3. "Persons who began drinking at each age group younger than 21 years (relative to those starting after age 21) were significantly more likely to have been injured while under the influence of alcohol." The injuries occur both before and after age 21.
4. Persons who develop alcoholism later in life may have had more adverse experiences in childhood such as psychological, physical and sexual abuse; domestic violence; and substance abuse by parents. Drinking earlier and more heavily may be an attempt to cope.
5. Persons who engage in a variety of deviant or illegal behaviors at an early age are more likely to continue them later in life.
6. Persons who begin drinking at an early age are more likely, when drinking, to place themselves in situations that pose risk of injury.
7. We should share with our adolescent patients information about risks associated with early-age drinking.

CONCLUSION

Drinking onset at ages younger than 21 years was associated with experiencing more alcohol-related injuries later in life.

JAMA September 27, 2000; 284; 1527-33 Original investigation, First author Ralph W Hingson, Boston University Scholl of Public Health, Boston Mass. **www.jama.com**

Comment:

Our young patients who begin smoking and drinking are calling out for help. We must heed their cry. RTJ

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9-7 CHANGES IN DIET, WEIGHT, AND SERUM LIPID LEVELS ASSOCIATES WITH OLESTRA CONSUMPTION.

The past few decades have seen an unprecedented increase in the availability of specially manufactured low-fat and non-fat foods.

At the same time, there has been a notable increase in prevalence of obesity in the US, where over half of the citizens are overweight or obese.

Did introduction of these new low-fat and low-fat foods have any beneficial effect on health and nutritional status of Americans?

Of particular interest is the effectiveness of newly introduced foods made with the non-energy fat substitute olestra.[1] Olestra containing foods are substantially lower in energy than their full-fat counterparts. If olestra containing foods are substituted for full-fat foods, energy and fat intakes will decrease.

This study examined the association between 1) olestra consumption and 2) intakes of energy, fat, and cholesterol, and changes in weight and lipid values.

Conclusion: Persons who included olestra-containing foods in their diet benefited by reduction of weight and improvement in lipid profiles.

STUDY

1. Obtained data from a cohort of 335 participants in the Olestra Post-Marketing Surveillance Study.
2. Assessed diet, weight, and lipid levels before and 1 year after olestra containing foods were made widely available.
3. Categorized olestra intake in the past month as: 1) none; low (0 to 0.4 g/d); moderate (0.4 to 2 g/d);

and heavy (> 2 g/d).

RESULTS

1. Heavy olestra consumers significantly reduced dietary percentage of energy from fat by 3%; saturated fat by 1%.
2. Changes in weight and lipids:

	Weight (kg)	LDL-cholesterol (mg/dL)	HDL-cholesterol (mg/dL)
Baseline	79	117	41
Heavy consumers (> 2 g/d)	-0.55	-23	+5

(*Certainly these changes in lipid levels are clinically significant. RTJ*)

DISCUSSION

1. In this "real-life" setting, consumption of olestra-containing snacks was associated with decrease in intake of fat and cholesterol.
2. If olestra chips are consumed with high-fat high-cholesterol foods such as hamburgers, a significant reduction in absorption of cholesterol could occur.
3. No significant trends in reductions of fat soluble vitamins was observed.
4. Another study found no evidence that olestra was associated with increase in gi complaints.

CONCLUSION

Consumption of olestra, a new fat substitute, was associated with benefits on lipid profiles and a reduction in total fat intake.

Archives Int Med September 25, 2000; 160: 2600-04 Original investigation, first author Ruth E Patterson, Fred Hutchinson Cancer Research Center, Seattle, WA **www.archinternmed.com**

Comment:

1 Olestra is a fatty-acid ester formed by combining sucrose with a variety of long-chain fatty acids. It is not absorbed from the gi tract and is energy-free.

Olestra potato chips contain 8 g of olestra per oz. (Personal communication Ruth Patterson.) The standard serving on the bag label is 1 oz (about 17 chips). It would be easy to consume more than 2 g at lunch. I found it tasty and not different from standard potato chips. RTJ

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9-8 WHOLE GRAIN CONSUMPTION AND RISK OF ISCHEMIC STROKE IN WOMEN.

Known risk factors for development of stroke include hypercholesterolemia, hypertension, obesity, and diabetes. All can be modified through dietary modification. "Primary prevention holds much promise."

Several epidemiological studies have associated higher rates of specific nutrients with a lower risk of cardiovascular disease **(CVD).** Higher intake of whole grain is reported to be associated with a lower risk of coronary disease.

This study asks — is risk of stroke related to whole grain intake?

Conclusion: Higher intake of whole grain was related to a lower risk of ischemic stroke.

STUDY

1. Nurse's Health Study entered over 75 000 women age 38 to 63 in 1984. All were free of diagnosed diabetes, coronary disease, and stroke.
2. Completed food-frequency questionnaires periodically. Whole grain foods included dark bread, whole grain breakfast cereal (25% or more whole grain or bran), brown rice, popcorn, cooked oatmeal, and bran.
3. Main outcome measure by quintile of consumption — incidence of ischemic stroke.
4. Follow-up = 12 years.

RESULTS

1. During follow-up 352 confirmed incident cases of ischemic stroke occurred.
2. There was an inverse association between whole grain intake and risk of ischemic stroke:
   Age-adjusted relative risks lowest to highest quintile of intake:
   1.00; 0.68; 0.69; 0.49; and 0.57
3. The inverse relationship was consistently observed among subgroups of women who never smoked, did not drink alcohol, did not exercise regularly, and who did not use hormone replacement therapy.
4. No significant relationship between *total* grain intake and ischemic stroke.
5. No association with hemorrhagic stroke.

DISCUSSION

1. There was a 40% lower risk of ischemic stroke in those with high-whole-grain intake compared with those consuming little. The apparent protective effect persisted after accounting for known risk factors for CVD.
2. The protective effect may involve multiple biological pathways. Whole grains contain abundant antioxidants, minerals, phytochemicals and fiber.

3. Most grains consumed in the US are processed and refined. (eg, sweet rolls, cakes/deserts, white bread, pasta, muffins, biscuits, refined cereals, white rice, pancakes, pizza.)
4. In the cohort, whole grains accounted for only one third of the servings of total grains, or a median of one serving daily.
5. Even those in the top quintile intake barely approached 3 servings daily.
6. Replacing refined grains with whole grains by even one serving daily may have significant benefits in reducing the risks of ischemic stroke.

CONCLUSION

Higher intake of whole grain foods was associated with a lower risk of ischemic stroke independent of known risk factors for CVD.

JAMA September 27, 2000; 284: 15 34-40 Original investigation, first author Simin Liu, Brigham and Women's Hospital, Boston Mass. **www.jama.com**

Comment:

To put this into perspective— in absolute terms, by my calculation from their data (*p 1538*), highest consumption of whole grain was associated with 12 fewer ischemic strokes per 100 000 women over 12 years. Or about one per 100 000 per year. To this must be added the reduced incidence of coronary events. RTJ

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9-9 HIGH BLOOD PRESSURE AND DIABETES MELLITUS

Are All Antihypertensive Drugs Created Equal?

The co-existence of diabetes and hypertension is devastating. Risk of stroke or any cardiovascular event is almost doubled. Lowering BP markedly decreases risk.

Since ACE inhibitors prevent renal deterioration in patients with diabetes they have been considered the drug of first choice. However, two recent large studies showed that calcium blockers and beta-blockers also reduce cardiovascular events in diabetic-hypertensive patietns. This raises the question — are ACE inhibitors indeed superior?

This study asks — are the available antihypertensive drugs equipotent in reducing BP and risk of cardiovascular events?

Conclusion: Low-dose diuretics, beta-blocker, calcium blockers, and ACE inhibitors were equally effective in reducing morbidity and mortality.

STUDY

1. MEDLINE search found 8 prospective, randomized trial of more than 12 months duration that evaluated the effect of drug treatment on morbidity and mortality in diabetic-hypertensive patients.

RESULTS

1. The study confirmed the increased risk of combined diabetes-hypertension for cardiovascular events, cardiovascular mortality and total mortality. (Relative risk = 2 to 3 compared with patients with hypertension alone.)
2. Lowering BP to less than 130/85 reduced risk significantly more than reduction to higher levels.
3. Tight control of BP also reduced risk of *micro*-vascular events (as well as *macro*-vascular).
4. Four prospective studies comparing each of 4 drugs with placebo found all drugs effectively reduced cardiovascular events and mortality.
5. Two studies compared ACE inhibitors with calcium blockers. ACE inhibitor therapy resulted in fewer primary end points and fewer myocardial ischemic attacks.

DISCUSSION

1. The co-existence of hypertension with diabetes doubled risk of cardiovascular events and mortality.
2. Intensive lowering of BP is associated with significant reduction in end-points. "In these patients, intensive BP control is more beneficial than tight glucose control."
3. ACE inhibitors have been considered the drugs of choice in diabetes-hypertension since they have beneficial effects on renal function above and beyond those simply due to BP control. They are also reported to be associated with fewer cardiovascular events than calcium blockers. Nevertheless, calcium blockers are beneficial.
4. To achieve BP less than 135/85, more than 60% of patients required combination therapy. Combination therapy may be more beneficial than monotherapy in reducing risk .

CONCLUSION

Intensive control of BP in patients with combined diabetes-hypertension to levels below 130/85 reduces risk of cardiovascular events. All 4 drug classes — diuretics, beta-blockers, ACE inhibitors, and calcium blockers — are effective.

Most patients with require combined therapy to obtain BP goal of 130/85

Archives Int Med September 11, 2000; 160: 2447-52 Original investigation, first author Ehud Grossman, Chaim Sheba Medical Center, Tel-Hashomer, Israel. **www.archinternmed.com**

Comment:

Many of the studies cited have been abstracted in *Practical Pointers*. What are the final practical points?

1. Treatment of hypertension in patients with diabetes requires stricter control than usual, with a target of at least 130/85. This includes patients with isolated systolic hypertension. Target may be difficult to achieve and usually requires double- or triple-therapy.
2. All 4 classes of drugs are beneficial. We might tilt toward ACE inhibitor as first drug. Captopril [generic] is inexpensive. My pharmacy quotes $8.17 for 100 25 mg tablets.
3. What second drug to add if there special indications? I would tilt toward diuretic. In elderly hypertensive patients, diuretics were superior to beta-blockers. (Citation # 42). Beta-blockers would be 3rd. Calcium blockers 4th.

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9-10 OBESITY SURGERY — ANOTHER UNMET NEED

It is effective but prejudice is preventing its use.

For patients with morbid obesity (BMI > 40 [1]) a conservative approach to weight control is doomed to failure.

About 1-2% of people in the UK are morbidly obese. The disease is often fatal. They have only a 1 in 7 chance of reaching their normal life expectancy

Good results have been obtained from surgery in these patients. The National Institute of Health in the United States has suggested that surgery is the most effective treatment for selected patients who are morbidly obese. Selection criteria for surgery include: BMI of > 40, or 35 to 40 in patients with serious co-morbid conditions that are treatable by weight loss: being obese for at least 5 years; having had a conservative program which failed; having no history of alcohol abuse or major psychiatric illness; between ages 18 to 55 with an acceptable operative risk.

The surgery must be delivered in a multidisciplinary environment.

Studies from Scotland matched 2000 obese patients receiving surgery with 2000 managed conservatively. Surgery was overwhelmingly better in improving quality of life, controlling high BP and diabetes, reducing atherosclerosis, improving rates of employment, and reducing health-related costs. Other benefits include improvement of lipids, sleep apnea, joint problems, gi reflux, urinary incontinence, and asthma.

Yet few operations are conducted in the UK. Few surgeons are trained to treat obesity. Society is ignorant and prejudiced against patients with morbid obesity. There is failure to understand that obesity

needs treatment just like any other disease. Some doctors consider obesity surgery to be a waste of resources.

Data from the international register of obesity surgery shows that, at 12 months, banding gastroplasty and gastric bypass result in a mean loss of 50 to 75% of excess weight with an operative mortality of 0.17%. Over 90% had no morbidity from surgery. Laparoscopic surgery has been introduced and reports over 50% loss of excess weight which was maintained for at least 6 years.

Comorbidity decreases as a result of even modest weight loss. **2**

Prejudice against surgery is associated with a low priority. Insurance companies may not pay for the procedure.

"An obesity surgeon should be available in all large hospitals together with the relevant multidisciplinary team."

BMJ September 2, 2000; 321: 523-24 Editorial by John Baxter, University of Wales, UK

www.bmj.com/cgi/content/full/321/7260/523

1 Weight in kg / height in meters^2

2 Any partial return of weight toward normal is beneficial.

Comment:

We should stress to our overweight patients that even a modest weight loss reduces risk of complicating illness. They do not have to gain normal weight. RTJ

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RECOMMENDED READING

9-11 END-OF-LIFE CONVERSATIONS

Evolving Practice And Theory

This article examines the evolution of, and the need for, "end-of-life conversations".

"For patients and their families facing advanced illness, the medical interventions that lie ahead are largely determined through a series of conversations they have with their physicians and other health care providers. These discussions occur between initial diagnosis and death and include many emotionally charged topics, such as unfavorable prognoses and treatment failure, treatment choices and family response to them, advanced care planning, concerns about one's ability to cope, life's goals and other life-closure issues, anticipatory mourning, and the meaning of illness and the suffering it creates. When these often difficult discussions are avoided or are managed poorly, the quality of remaining life for patients can be seriously jeopardized."

The writers conclude:

1. Where culturally appropriate, end-of-life conversations should become a routine part of health care delivery. They cannot be initiated solely in response to disclosures by patients because patients as well as health care professionals tend to avoid these uncomfortable discussions.

2. Structured and content-based interventions are needed to ensure that critical aspects of the patient's physical, psychological, and spiritual experience are not excluded from care.

3. Additional training of health-care providers is needed. No single health care professional can undertake all aspects of this challenge.

4. Advance care planning must be viewed, not as a final outcome, but as one component in a series of ongoing conversations that together can assist the patient with advanced illness to approach death in accord with his or her own values and wishes.

"We conclude that end-of-life conversations must become a routine, structured intervention in health care, and that advanced care planning is best viewed as one component in a series of ongoing end-of-life discussions."

JAMA September 27, 2000; 284: 1573-78 "The Patient-Physician Relationship", commentary, first author Dale G Larson, Santa Clara University, California. **www.jama.com**

Comment:

The authors stress that the process should be patient-centered. We must be ever aware of the patient's cultural background. Conversations must be tailored individually. Primary care physicians must call on the time and expertise of others (clergy, nurses, family, friends). I believe the primary care clinician can take a lead in opening the conversation by gentle indirect questions seeking the need and wishes of the patient to enter such discussions. The conversations should be ongoing, giving the patient time to consider what concerns he may wish to discuss. RTJ

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9-12 HORMONE REPLACEMENT THERAPY AND PERIPHERAL ARTERY DISEASE

Evidence from observational studies suggests that hormone replacement therapy **(HRT)** reduces morbidity and mortality from coronary artery disease. What about peripheral vascular disease **(PVD)?**

This study investigated the association between use of HRT and presence of atherosclerosis in the arteries of the lower extremities.

Conclusion: HRT was associated with a decreased risk of peripheral vascular disease.

STUDY

1. Population based study entered over 2000 naturally menopausal women age 55 to 80. (Mean age = 66)
2. Defined PVD as an ankle/arm systolic BP index **(AAI)** lower than 0.9. (Eg, brachial systolic BP 100 mm Hg/ankle systolic BP < 90 mm Hg.)
3. Determined number of subjects who had used HRT for 1 year or more. (16% of subjects.)

RESULTS

1. Mean AAI was 1.08. About 10% had AAI < 0.9.
2. Age, systolic BP, total cholesterol, glucose levels, and smoking were all significantly higher in women with PAD.
3. Of 169 long term users 13 (8%) had PVD; of 1837 non-users, 247 (13%) had PVD. Adjusted relative risk = 0.48
4. No association with use of less than 1 year.
5. Adjustment for multiple confounding factors did not change the results.

DISCUSSION

1. The AAI gives a good indication of atherosclerosis in the lower limbs.
2. The authors admit the possibility of selection bias. Part of the apparent benefit may have been due to pre-existing characteristics of the HRT users.

CONCLUSION

In this population-based study, postmenopausal women who took HRT for a year or more had a decreased risk of PAD.

Archives Int Med September 11, 2000; 160: 2498-02 Original investigation, first author Iris C D Westendorp, Erasmus University Medical School, Rotterdam, Netherlands **www.archinternmed.com**

Comment:

I do believe, in general, women who take HRT achieve some decrease in risk of atherosclerotic disease. The question is — why? At least part of the benefit is due to the "health user" effect. The question then is — how much? After years of investigation, the question is still not answered. RTJ

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9-13 MULTIPLE COMPLEX CORONARY PLAQUES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Rupture of coronary artery plaques causes acute myocardial infarction **(MI).** The unstable plaque is often considered to be a single lesion on arteriography. These investigators postulated that, since coronary atherosclerosis is diffuse, plaques might be expected to develop in a multifocal pattern, resulting in multiple complex plaques in different locations. Any one of these lesions might progress to total occlusion and MI.

This study was designed to document the incidence of multiple complex plaques in patients with acute transmural MI, and to determine their influence on outcomes.

Conclusion: Patients with acute MI may harbor multiple complex plaques that are associated with adverse outcomes. Plaque instability may be a widespread process throughout the coronary arteries.

STUDY

1. Analyzed angiograms of over 250 consecutive patients for coronary plaques characterized by thrombus, ulceration, plaque irregularity, and impaired flow.
2. Lesions were considered complex if they caused at least 50% stenosis and had two or more morphologic features: filling defects; plaque ulceration; plaque irregularity; and impaired flow. (*See text p 915*)

RESULTS

1. Identified single complex coronary plaques in 60% and multiple complex plaques in 40%.
2. Patients with multiple complex plaques were less likely to undergo primary angioplasty, and to more commonly require bypass surgery. They also had greater depression of left ventricular function.
3. During the following year, multiple complex plaques were associated with an increased incidence of acute coronary syndromes, repeat angioplasty, and bypass surgery.

DISCUSSION

1. . "The presence of coronary plaques with complex morphologic features is the angiographic hallmark of unstable coronary syndromes, and correlates with pathologic plaque rupture and thrombus." Progression of stenosis and clinical instability are characteristic of such lesions. There is a striking association between complex morphologic features and clinical instability. Patients with acute MI may harbor multiple complex coronary plaques which are associated with adverse clinical outcomes.
2. This . . . "supports the concept that plaque instability is not merely a local vascular accident, but probably reflects a more generalized pathophysiologic process with the potential to destabilize atherosclerotic plaques throughout the coronary tree".
3. Angiographic natural-history studies in patients with unstable angina demonstrate rapid progression, not only of the initial culprit lesion, but also of the non-culprit complex lesions.

4. The presence of multiple complex coronary plaques identifies a subgroup of patients at increased risk for recurrent ischemia, even after successful initial PTCA.

CONCLUSION

Patients with acute MI may harbor multiple complex coronary plaques that are associated with adverse clinical outcomes. Plaque instability may occur as a widespread process throughout the coronary arteries.

NEJM September 28, 2000; 343: 915-22 Original investigation, first author James A Goldstein, William Beaumont Hospital, Royal Oak, Michigan. **www.nejm.com**

Comment:

So . . . what is the practical point? Atherosclerosis is a widespread disease. Not only of the coronary arteries, but also of carotid, renal, peripheral arteries, and the aorta. When a coronary lesion is identified, we can be certain that lesions are present elsewhere in the arterial tree as well as elsewhere in the coronary tree. We are dealing with a wide-spread, not a localized disease. Medical therapy, not surgery, is the ultimate answer to primary prevention and treatment.

We now have excellent measures to prevent or delay the process. If these fail and individuals develop clinical disease, we still may have a good chance at stabilizing the disease with all-out medical therapy and life-style changes. RTJ

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REFERENCE ARTICLE

9-14 CURRENT ROLE OF PLATELET GLYCOPROTEIN IIB/IIIA INHIBITORS IN ACUTE CORONARY SYNDROMES

Acute coronary syndromes **(ACSs)** span the pathological continuum from unstable angina to non-Q-wave myocardial infarction (MI).[1] Platelet aggregation on unstable plaques forming platelet-rich thrombi, which subsequently embolize distally, are central to understanding the pathophysiology of ACSs. Platelet aggregation occurs in the initial ischemic event as well as in recurrent events. Unstable plaques may persist for more than a month after an acute MI.

A glycoprotein receptor, termed GpIIb/IIIa exists on the surface of platelets. Activation of this receptor is the final common pathway in the process of platelet aggregation.

This study defined the optimal role of GpIIb/IIIa inhibitors in treatment strategies of ACSs.

Conclusion: GpIIb/IIIa therapy has a prominent therapeutic role.

STUDY

1. MEDLINE search found 10 randomized, double-blind placebo-controlled trials of GpIIb/IIIa inhibitors in ACSs.

RESULTS

1. Three classes of GpIIb/IIIa inhibitors are available for intravenous use: abciximab (*ReoPro*) , eptifibatide (*Integrilin*), and tirofiban (*Aggrastat*). Each one has data demonstrating improved outcomes in patients with ACSs
2. Therapy is safe, and with proper precautions, bleeding risks can be minimized.
3. Biological differences exist between the 3 drugs, but no head-to-head comparisons have been made.
4. GpIIb/IIIa blockade during percutaneous coronary intervention:
   Abciximab (with and without stent placement) resulted in a 60% reduction in rate of 30-day death, MI, and urgent revascularization. Bleeding risk was reduced when lower doses of heparin were used.[2] Low-molecular-weight heparin appears superior to unfractionated heparin. Benefit may be especially evident when troponin levels are increased.
5. GpIIb/IIIa inhibitors for medical management:
   Pooled results from 4 large trials reported a reduction of 1.6% in death and non-fatal MI at 30 days in patients receiving medical management including heparin and aspirin. Reduction in death and MI were more evident in patients with positive troponin tests.
6. Treatment strategies:
   "The benefits of GpIIb/IIIa inhibitors in stabilizing patients with ACSs has yet to be fully realized." Early treatment with GpIIb/IIIa inhibitors with non-ST elevation ACS would be expected to improve outcomes. Treatment beginning within 24 hours of symptom onset was associated with a 2% absolute reduction in death and non-fatal MI. Indeed, there appears to be a graded effect, with patients treated at the earliest having greater benefit. Again, those with positive troponin appear to gain maximal benefit.

CONCLUSION

Intravenous GpIIb/IIIa inhibition therapy has greatly enriched the therapeutic armamentarium for patients with ACSs. Administered at the time of urgent angiography with PTCA, coronary revascularization, or empirically in the emergency department at presentation, these agents build on the antithrombotic template of aspirin and heparin.

GpIIb/IIIa inhibition merits a prominent role in the management of ACSs, either medically or in conjunction with PTCA.

JAMA September 27, 2000; 284: 1549-58 "Clinical Cardiology" Systematic review by Deepak L Bhatt and Eric J Topol, Cleveland Clinic foundation, Cleveland Ohio. **www.jama.com**

Comment:

1 I recently encountered what I believe is a more accurately descriptive term — Unstable angina non-ST elevation myocardial infarction (UANSTEMI).

2 Platelet transfusions can reverse any excess bleeding.

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REFERENCE ARTICLE

9-15 THE ROLE OF THE INTERLEUKIN-1-RECEPTOR ANTAGONIST IN BLOCKING INFLAMMATION MEDIATED BY INTERLEUKIN-1

Cytokines are low molecular weight proteins secreted by various cell types. They regulate the intensity and duration of immune responses and mediate cell communication. As the chemical structure of each cytokine is determined, it is designated as an interleukin and assigned a number. There are now at least 18 interleukins. Cytokines not yet fully defined chemically retain their original designation — eg, tumor necrosis factor.[1]

I abstracted this article to learn more about these new molecules which are leaving the realm of basic research and entering the mainstream of clinical medicine at a rapid pace.

" They didn't have that when I was in medical school." RTJ

Blocking the activity of specific cytokines attenuates the effects of the cytokine on disease or halts its progression

Interleukin 1 **(IL-1)** is produced normally in response to inflammation. When it occupies a receptor on various cells, it results in the production of secondary substances that mediate inflammatory events. IL-1 induces release of platelet-activating factor, nitric oxide, prostaglandin E, chemokines (which facilitate emigration of circulating leukocytes), collagenases (which promote breakdown of cartilage), and activation of osteoclast precursors (which leads to increased bone resorption).

IL-1 receptor antagonists **(IL-1RAs)** occupy the receptors on various cells so that IL-1 cannot bind. Thus the biologic effect of IL-1 is attenuated. There is a natural balance between the proinflammatory activities of IL-1 and the ability of the IL-1RAs to keep the proinflammatory activities in check.

Both proteins are produced normally. There is a natural balance between the proinflammatory activity of IL-1 and the blocking effect of IL-1RAs . This keeps the effects of IL-1 in check.

IL-1 is a potential target of therapeutic intervention in a variety of inflammatory and autoimmune conditions. Blocking its effects with an IL-1RB reduces local inflammation of joints and bone erosions in patient with rheumatoid arthritis. It is being evaluated in clinical trials as a treatment for multiple sclerosis.

The increased production of IL-1 during an inflammatory disease contributes to the pathologic process by binding to and triggering its receptor. Normally enough IL-1 receptor antagonist is produced to hold the interleukin-mediated inflammation at bay. In cases of runaway inflammation there is an insufficient amount of IL-1-receptor antagonist to control the activity of IL-1. Administration of exogenous IL-1RA should ameliorate inflammatory disease.

NEJM September 7, 2000; 343: 732-34 "Clinical Implications of Basic Research" Commentary by Charles A Dinarello, University of Colorado Sciences Center, Denver. **www.nejm.com**

1 . Blockers of tumor necrosis factor are now being used to treat Crohn's disease and rheumatoid arthritis. As far as I know the molecular structure of tumor necrosis factor is not yet known. Thus it is not designated as an interleukin.

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9-16 RISKS OF INTERRUPTING DRUG TREATMENT BEFORE SURGERY.

Many of the millions of patients undergoing surgery each year are taking therapeutic drugs prescribed for concurrent diseases. (Many are also taking "recreational drugs".) Abrupt interruptions lead at best to a loss of their positive therapeutic benefits, and at worst to rebound exacerbations of diseases.

Surgery, major abdominal surgery in particular, can cause patients to abstain from their usual drug treatment. After major abdominal surgery, gastric emptying is delayed, making administration of drugs by the oral route unreliable.

Adaptive and mal-adaptive physiological and psychological stresses related to surgical trauma may make surgical patients more vulnerable to complications caused by abstention from their drug treatments.

However, there is little systematic evidence that quantifies the risk of abrupt withdrawal of therapeutic drugs in the postoperative setting.

A recent study of 1000 admissions reported a higher incidence of perioperative complications among patients who took therapeutic drugs. Most drugs taken were not related to the surgery; half were cardiovascular drugs. Only 8% were taking drugs traditionally recognized as surgically important, such as corticosteroids and drugs for diabetes.

There was a significant association between abstinence from these therapeutic drugs and adverse outcomes. There was also a highly significant association between the duration of time without medicine and the complication rates. Patients taking ACE inhibitors seemed to be at particular risk.

What should be done?

1. Allow the patient to continue medication until the day of surgery if possible.
2. Use alternatives to the oral route until the oral route is reestablished.
3. When alternative routes for administration of the specific drug involved are not available, a similar drug may be substituted.
4. Institute efforts to return gi tract function as soon as possible.

The problem of abrupt drug cessation is not sufficiently recognized. Drug information formularies should identify the best substitutes for drugs that cannot be given parenterally. Hospital pharmacists play an important role in providing guidance.

BMJ September 23, 2000; 321: 719-20 Editorial, first editorialist David W Noble, Grampian University Hospitals, Aberdeen Scotland. **www.bmj.com/cgi/content/full/321/7263/719**

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9-17 COMPARISON OF ST JOHN'S WORT AND IMIPRAMINE FOR TREATING DEPRESSION

Hipprocrates and Galen described the use of *Hypericum perforatum* (St John's wort) as a treatment against demonic possession.

A meta-analysis concluded that hypericum was more effective than placebo for depression. Is it as effective as other antidepressants?

This investigation compared efficacy and tolerability of *Hypericum perforatum with* imipramine (*Generic*) in patients with mild to moderate depression.

Conclusion: The two were therapeutically equivalent. Hypericum was better tolerated.

STUDY

1. Randomized, multicenter, double-blind trial entered 324 outpatients with mild to moderate depression.
2. Randomized to: 1) 75 mg imipramine (*Tofranil*; generic) twice daily, or 2) hypericum extract twice daily for 6 weeks. (The hypericum was extracted to 0.2% in ethanol and standardized by German methods. Imipramine dose was gradually increased to reach full therapeutic dose.)
3. Outcomes — changes from baseline in 3 depression scales.

RESULTS

1. Changes in scale of depression	Hypericum		Imipramine
Hamilton scale			
Baseline	22		22
6 weeks	12	(improvement)	13

2. Two other scales showed similar improvement in both treatment groups, there was no significant difference between groups.
3. However, on an anxiety-somatization scale there was a significant advantage for hypericum relative to imipramine.
4. Hypericum was better tolerated. Adverse events occurred in 37% of hypericum patients. (3% withdrew) compared with 63% of imipramine patients (16% withdrew).

DISCUSSION

1. The efficacy and safety of herbal remedies is not often subject to the systematic testing required of conventional drugs.[1]
2. Some evidence suggests that hypericum is better in relieving anxiety.
3. The possible interaction of St John's wort with other drugs must be considered.
4. "Hypericum should be considered for treating mild to moderate depression, especially in primary care."

CONCLUSION

This Hypericum extract was therapeutically equivalent to imipramine in treating mild to moderate depression. It was better tolerated than imipramine.

BMJ September 2, 2000; 321: 536-39 Original investigation reported by Helmut Woelk for the Remotiv/Imipramine Study Group **www.bmj.com/cgi/content/full/321/7260/536**

1 See also: "Garlic for Treating Hypercholesterolemia A Meta-analysis of Randomized Clinical Trials" Annals Int. Med. September 19, 2000; 133: 420-429 "The available data suggest that garlic is superior to placebo in reducing total cholesterol levels. However, the size of the effect is modest and the robustness of the effect is debatable. The use of garlic for hypercholesterolemia is therefore of questionable value."

Comment:

We traditional "scientific" clinicians are losing some of our skepticism about herbal remedies. But, doubts remain. We reject anecdotal reports. We do not understand how herbs work. They are not standardized. The active pharmacologic component(s) are not determined, and undoubtedly vary from batch to batch. They are available over-the-counter without regulation. Adverse effects may occur when providers

alter the contents. Interactions may occur when herbs are added to prescription medicines. Often the MD does not know what herbs patients are taking. Costs may actually be higher than standard prescription drugs, especially generics.

I think back 60 years when digitalis leaf was available in pill form. Attempts were made to standardize the dose. (Remember "cat units"?). Attempts are being made to determine the active chemical components of herbs and to standardize the dose. They will then be more willingly entered into conventional medical practice. RTJ

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REFERENCE ARTICLE

9-18 DIAGNOSIS AND TREATMENT OF CHRONIC ABACTERIAL PROSTATITIS:

A Systematic Review

A thoughtful and extensive summary of a wide and complex body of literature. It concludes: "There is no gold standard diagnostic test for chronic abacterial prostatitis, and the methodologic quality of available studies of diagnostic tests is low. The few treatment trials are methodologically weak and involved small samples. The routine use of antibiotics and alpha-blockers to treat chronic abacterial prostatitis is not supported by the existing evidence."

Annals Int Med September 5, 2000; 133: 367-81 Review, first author Mary McNaughton Collins, Massachusetts General Hospital, Boston. **www.annals.org**

Comment:

Another good example of the limitations of "evidence-based medicine". Many conditions and diseases have no helpful systematic evidence to help the primary care clinician. She nevertheless must deal as best she can with the problems patients present.

I believe that many patients with "chronic prostatitis" will continue to suffer symptoms despite symptomatic treatment. Many may seek "alternative treatments". RTJ

NOTICE

Practical Pointers is available each month as an attachment to e-mail. Anyone wishing to receive it in this manner, please notify the editor at rjames6556@aol.com