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SYSTOLIC HYPERTENSION IN OLDER PERSONS: A REVIEW

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HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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HIGHLIGHTS AND EDITORIAL COMMENTS SEPTEMBER 2004

9-1 SYSTOLIC HYPERTENSION IN OLDER PERSONS

Systolic hypertension (*SH*, or preferably isolated systolic hypertension *ISH*) is defined as a systolic BP of 140 and above and a diastolic BP less than 90. Stage one ISH is defined as systolic 140-159, and diastolic less than 90.

It is the most common form of hypertension in elderly persons. It is a major public health issue. In persons over age 60, SH is a much more important cardiovascular risk factor than diastolic hypertension.

Guidance for treatment comes primarily from observational data which document increased risks in patients with ISH. The Framingham study reported a greater risk of development of cardiovascular disease; coronary heart disease; stroke; and heart failure in patients with stage one ISH (RRs = 1.47; 1.40; 1.42; and 1.60) compared with normotensive patients. (*Would it then be reasonable to assume that lowering BP would reduce risks? But the study did not consider effect of treatment. RTJ*)

In one trial, the benefit of active treatment compared with placebo reached its maximum at age 80. The RR for stroke in the oldest age group was 0.53 vs 0.74 in age 60-69. “Evidence suggests that older patients do benefit from treatment.”

While there is strong evidence of benefit to guide treatment of ISH at a systolic BP of 160 and above, the evidence for treating BP between 140 and 159 is less strong. JNC 7 states that a BP higher than 140/90 warrants drug therapy, irrespective of age. But— “No randomized clinical trial evidence is available to demonstrate that reducing a BP of 140 to 159 in older persons (to under 140) reduces morbidity or mortality.” Although JNC 7 states that patients should be treated to targets of less than 140 in most cases, and less than 130 for diabetes or chronic renal disease, there are no clinical trial data to support this recommendation.^a

However, treatment should not be withheld solely according to advanced age. This group has especially high cardiovascular risk. Therapy should be determined by balancing potential benefits of treatment with individual patient preference and tolerance to therapy.

a This does not suggest that there is evidence that reducing systolic BP below 140 does not reduce risk of cardiovascular complications. I believe there is a linear relationship between BP and risk, extending to the lower systolic levels. The problem is to judge how vigorously and rapidly drug treatment should be applied.

This is an important clinical consideration for primary care. I believe many elders with ISH are overtreated. Some articles suggest that clinicians are not doing a good job of controlling hypertension if target levels are not reached.

Caution in using drastic BP-reduction in elderly patients. Go slow and go low. They are sensitive to adverse effects of drugs as well as to rapid reduction of BP. I believe many patients with ISH (especially the very elderly) are over-treated. A home BP monitoring device would be helpful in guiding treatment. Home BP may be lower than office BP and allow reduction in dose of drugs. I believe slight differences in the BP response reported between different drugs are not as meaningful as adverse effects. I would choose the lowest dose(s) of the least

expensive drug and very gradually adjust as tolerated. I would try to get the systolic below 160, and would be content at this level if pushing the dose higher were not well tolerated.

The cause of elevation of systolic BP in older persons is increased stiffness and lack of compliance of their arterial system. Reducing the systolic BP does not remove the cause. It may reduce incidence of CVD by lessening stress and shear forces on the arteries. RTJ

9-2 COST-RELATED MEDICATION UNDERUSE

Patients often restrict their use of prescribed medications because of cost. Those who have chronic conditions, and require long-term medication are most vulnerable. Underuse has been associated with serious health consequences, increased emergency department visits and nursing home admissions, and decrements in self-reported health status.

This nationwide survey identified of a group of patients with chronic illnesses who reported underuse of medication and the reasons for underuse, mostly due to costs. About 1/3 never discussed this problem with their doctors. Most patients were never asked about cost problems. When patients did talk about the costs, the majority found the conversation helpful. However, many stated their prescription was never changed to a generic or to a less expensive alternative. They received no information about which drug(s) might be less necessary and might be excluded. Few patients were given other forms of assistance such as referral to a social service agency, information about programs that help pay drug costs, or where to purchase less expensive medication.

“Very few chronically ill patients who restrict their medication use because of cost appeared to be receiving assistance from their health care providers.”

“Clinicians should take a more proactive role in identifying and assisting patients who have problems paying for prescription drugs.”

Clinicians consider the benefit/harm ratio of all drugs they prescribe. I believe the ratio is better expressed as benefit/harm-cost. When a prescribed drug is expensive it would be appropriate to mention this to even the most affluent patient. And to routinely discuss cost considerations with those less economically advantaged. Rapport with social services is most helpful.

This study raises a most important consideration in these days of patient-centered medicine. When negotiating a treatment plan with the patient, we must arrive at a conclusion which the patient understands and is willing and able to follow. An expert consultation is worthless if the patient cannot or will not follow the prescription for any reason, including costs.

I believe most doctors have little knowledge about costs of drugs and procedures they prescribe. They should learn. The lowest cost effective and safe program should be offered to all patients, regardless of their economic status.

I am convinced the American public is over-charged and over-medicated

The drug store pages on the internet are rapidly accessible and list prices. Drugs ordered over the internet may be less costly than at the local pharmacy. I believe much of the cost of drugs with a large therapeutic index (eg, statins) can be reduce by use of a pill cutter. An 80 mg pill may cost the same as a 20 mg pill. When cut into quarters, the cost would be reduced by 75%. It makes little difference in the effectiveness and safety of many

drugs whether the daily dose is a few milligrams above or below the prescribed dose. This is not applicable to drugs with a narrow dose-range for safety and effectiveness. RTJ

9-3 ASSOCIATION OF HEMOGLOBIN A1C WITH CARDIOVASCULAR DISEASE AND MORTALITY IN ADULTS

Diabetes raises the risk of *macro*-vascular disease as well as micro-vascular disease. Evidence suggests that the relation between plasma glucose and macro-disease (cardiovascular disease; **CVD**) is continuous and does not have obvious thresholds.

In this study of over 10 000 subjects, the risk of CVD, CHD and mortality increased continuously as HbA1c rose. Cardiovascular disease events increased continuously from 6.7 per 100 men with HbA1c less than 5% to 35 per 100 men with HbA1c over 7%. The risk for CHD was significantly increased in those with HbA1c 5.0% to 5.4% compared with those with HbA1c concentrations less than 5%. This included individuals *without* diabetes.

Each increase of HbA1c of 1% was associated with a relative risk of 1.26 for death from any cause. The relationship was apparent in persons without known diabetes. (Only 193 subjects had known diabetes.)

HbA1c levels were significantly associated with all-cause mortality and coronary and cardiovascular disease even below the threshold commonly accepted for the diagnosis of diabetes. Each increase of HbA1c of 1% was associated with a 20% to 30% increase in mortality and cardiovascular events. The gradient was apparent through the population range from less than 5% up to 6.9%.

Subjects with HbA1c over 7% made up 4% of the sample and contributed about 25% of the excess mortality. Reduction in HbA1c levels in persons *without* diabetes may lessen their risk.

The metabolism of glucose is related to risk of cardiovascular disease. A healthful lifestyle should include attempts to control postprandial glucose levels in patients without diabetes as well as those with diabetes. Diets containing a low glycemic load are an important part of healthy living. RTJ

9-4 GLYCOSYLATED HEMOGLOBIN: FINALLY READY FOR PRIME TIME AS A CARDIOVASCULAR RISK FACTOR.

The societal burden of the diabetic epidemic is being fueled by our current lifestyle. Diabetes is just the measured tip of a much larger “dysglycemic iceberg”.

It is now clear that fasting and 2-h PG levels well below the diabetes cutoffs are cardiovascular risk factors. And that a progressive relationship between PG and CVD risks extends from normal glucose levels right into the diabetic range, with no clear lower threshold.

Evidence is accumulating that HbA1c is a progressive risk factor for CVD in people *without* diabetes as well as people with diabetes. A HbA1c level of 6.59% in a *non-diabetic* person predicts a higher CVD risk than a HbA1c of 5.5%. Even after excluding individuals with a HbA1c level of 7% and greater, with diabetes, and with a history of heart disease, the increase in risk for CHD, CVD, and total mortality for every 1% rise in HbA1c was 40%, 16%, and 26% respectively.

We can conclude that HbA1c is an independent and progressive risk factor for incident CVD regardless of diabetes status. “Glycosylated hemoglobin level can now be added to the list of other clearly established

indicators of CVD risk.” “The presence or absence of diabetes is likely to become less important than the level of glycosylated hemoglobin in the assessment of CVD risk. Reducing HbA1c in both diabetic and non-diabetic persons may reduce cardiovascular risk.”

It will be interesting to find out the relative risks of HbA1c and hyperinsulinemia compared with lipids. Could it be that markers of a stressed glucose-insulin metabolism will become clinical risk indicators as important as LDL-c and HDL-c? This would include the 2-hour postprandial glucose as well as the HbA1c level. Could food sugars become as important a risk factor as saturated fats? Excess sugar intake is related to obesity and the metabolic syndrome, and in turn to hypertension, hyperinsulinemia, and dyslipidemia.

I believe, at the present stage of our knowledge, we should consider aberrant glucose metabolism an important risk factor for CVD and act on it. RTJ

9-5 MEDITERRANEAN DIET, LIFESTYLE FACTORS, AND 10-YEAR MORTALITY IN ELDERLY EUROPEAN MEN AND WOMEN

Because of the cumulative effect of adverse factors throughout life, it is particularly important for older persons to adopt diet and lifestyle practices that minimize their risk of death and morbidity and maximize their prospects for healthful aging.

This study investigated the association of dietary patterns and lifestyle factors with mortality in elderly men and women in 11 European countries.

Followed a cohort of over 1500 apparently healthy men and over 800 apparently healthy women age 70-90 (mean = 75) at baseline.

Investigated the single and combined effect of 4 factors (Mediterranean diet, being physically active, moderate alcohol use, and non-smoking) on mortality.

Each of the 4 factors was individually associated with lower mortality rates from CHD, CVD, cancer, and all causes.

Individuals with 2, 3, or 4 low-risk factors had a significantly and progressively lower mortality compared with individuals with 0 or 1 low-risk factors.

Among individuals age 70 to 90, adherence to a MD and healthful lifestyles was associated with a more than 50% lower risk of mortality over 10 years.

There was no indication of the life-style habits in these persons during their earlier life. I suspect the habits were the same when they were young as when they aged.

Have we finally found the Fountain of Youth, or at least taken a sip from it? RTJ

9-6 FRAILITY—AND ITS DANGEROUS EFFECTS—MIGHT BE PREVENTABLE.

The differences between a 70-year-old who is robust and one who is frail are easily detectable. Frail old people are more vulnerable, withdrawn, unsteady, and weak. “In short, doctors know frailty when they see it.” The newer view moves away from the common view that frailty is an inevitable part of old age toward a new view of frailty as an avoidable condition. Some experts believe that frailty may some day be an official coded

disease, replete with FDA-approved treatments. It is likely that the diagnosis will be based on both laboratory tests and physical findings.

A recent study defined frailty as having at least 3 of 5 attributes: unintentional weight loss; muscle weakness; slow walking speed; exhaustion; and low physical activity. These findings persist in some old persons despite exclusion of the most common chronic illnesses. About 7% of persons older than 65, and 20% of those over age 80 may fit the definition of frailty. A screening tool for frailty has been described—gait speed, chair stands, and tandem balance.

“There is a biology of frailty that may be independent of age and specific disease states.”

I enjoyed abstracting this article. Although somewhat “far out”, it focused on a concept I had not thought about beforehand. We continue to search for the Fountain of Youth.

Can we die of “old age”? Do we require a more definitive cause of death on the death certificate?

I believe that, despite identical beneficial life-styles, some individuals become frailer at a younger age than others. There is something different between them. This is especially evident to resident of retirement communities and nursing homes.

As many studies have demonstrated, healthful lifestyles can delay the onset of frailty and prolong a productive and enjoyable life span. RTJ

9-7 PREVALENCE OF MIGRAINE IN PATIENTS WITH A HISTORY OF SELF-REPORTED OR PHYSICIAN-DIAGNOSED “SINUS” HEADACHE.

“Sinus” headache may constitute one of the most common and misdiagnosed clinical presentations of migraine. Symptoms referable to the sinus areas are frequently reported during migraine attacks. They are not recognized as diagnostic criteria for migraine.

This study determined the presence of migraine-type headache (defined by the International Headache Society (IHS) classification of migraine) in patients with “sinus” headaches. The IHS states that chronic sinusitis is *not* validated as a cause of HA or facial pain unless it relapses into an acute phase.

The great majority of patients with a history of “sinus” HA were determined to have migraine-type HA. The presence to sinus-area symptoms may be a part of the migraine process. Overdiagnosis of “sinus” HA contributes to under-recognition of migraine. And undertreatment.

Certainly a clinical point worth considering. RTJ

9-8 PHYSICAL ACTIVITY, INCLUDING WALKING, AND COGNITIVE FUNCTION IN OLDER WOMEN

This study examined the relation of long-term regular physical activity, including walking, to cognitive function in a large cohort of women. Higher levels of activity were associated with better cognitive performance. On a global score combining results of all cognitive tests, women in the second through the fifth quintile of energy expenditures scored an average of 0.06, 0.06, 0.09, and 0.1 standard units higher than women in the lowest quintile

Compared with women in the lowest physical activity quintile, those in the highest quintile had a 20% lower risk of cognitive impairment.

“In this large prospective study of older women, higher levels of long-term regular physical activity were strongly associated with higher levels of cognitive function and less cognitive decline. This benefit was similar in extent to being about 3 years younger in age.” The association was not restricted to women engaging in vigorous activity. Walking the equivalent of at least 1.5 hours per week at a 20 to 30 minute per mile pace was also associated with better cognitive performance.

This is an interesting, provocative study. It is not proof of any relationship between physical activity and cognition. Observational studies cannot prove cause and effect. But I believe patients should be reminded of the many benefits of physical fitness. There is now suggestive evidence of improved cognitive function.

A companion article in this issue of JAMA (pp 1447-52) “Walking and Dementia in Physically Capable Elderly Men”, first author Robert D Abbott, University of Virginia School of Medicine, Charlottesville, comes to the same conclusion. RTJ

9-9 CLINICAL DETERMINANTS OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME.

Patients with IBS have a health-related quality of life (**HRQOL**) that may be significantly worse than some other chronic diseases such as diabetes and end-stage kidney disease.

This study identified a concise set of mental and physical factors in patients with IBS that might lead to physician’s gaining better insight into these patients.

Seven factors independently predicted *physical* HRQOL: 1) more than 5 physician visits per year; 2) tiring easily; 3) low in energy; 4) severe symptoms; 5) predominantly pain symptoms; 6) feeling that there is something seriously wrong with body; 7) symptom flares longer than 24 hours.

Other factors independently predicted *mental* HRQOL: 1) feeling tense; 2) feeling nervous; 3) feeling hopeless; 4) difficulty sleeping; 5) tiring easily; 6) low sexual interest; 7) IBS symptoms interfere with sexual interest.

HRQOL in patients with IBS is primarily lowered by *extraintestinal* symptoms rather than traditional gastrointestinal symptoms. By screening for predictors of HRQOL, physicians may be in a position to initiate effective, timely, and self-empowering therapy. Addressing HRQOL allows clinicians to better understand patient’s needs and modify care-seeking patterns.

Instead of focusing on physiological epiphenomena (stool frequency, stool characteristics, and subtype of IBS) physicians might better serve the patient by gauging *global* symptom severity, addressing anxiety, and identifying and helping the patient to eliminate factors contributing to chronic stress.

This begs the question – Exactly how should the busy primary care clinician respond to these suggestions?

A basic function of primary care is to get to know the patient as a person. Merely allowing the patient to recognize and ventilate these HRQOL problems and validating them may in itself be therapeutic. It does not follow necessarily that improving the patient’s HRQOL will reduce symptoms of IBS. Improving HRQOL in itself is beneficial.

While we continue to seek a pathophysiological basis for IBS and assess various new drug treatments, we already have a meaningful therapeutic approach. RTJ

ABSTRACTS SEPTEMBER 2004

No Strong Clinical Evidence of Benefit in Reducing Systolic to Below 140 in Patients with BP 140-159

9-1 SYSTOLIC HYPERTENSION IN OLDER PERSONS

Systolic hypertension (**SH**) is defined as a systolic BP of 140 and above and a diastolic BP less than 90. It is a major public health issue which affects predominantly older persons. In persons over age 60, SH is a much more important cardiovascular risk factor than diastolic hypertension. Control of SH should be the focus of treatment in this population.

In 1999, isolated elevation of systolic BP was the most common finding among patients being treated for hypertension (76%), compared with 1990-95 (57%).

This article reviews the literature on SH, and considers several clinical issues.

Evolution of Terminology and Definition of SH:

The term isolated systolic hypertension (**ISH**) was used for many years to describe an elevated systolic with a normal or low diastolic BP. Because of concerns that the word *isolated* may minimize the perceived health risk, many authors have adopted the term systolic hypertension to emphasize that this condition is an integral part of cardiovascular health.

Stage one SH is defined as systolic 140-159, and diastolic less than 90.

*(I think the term isolated systolic hypertension (**IHS**) is more descriptive and preferable. I will use this term in this abstract. RTJ)*

What is the evidence for BP reduction for patients with a systolic 160 and higher and a diastolic less than 90?

Three large trials have reported the effects of treating ISH in subjects over age 66 on risk of stroke.

Mean baseline BP was about 172/84. Drugs used: 1) primary: chlorthalidone (generic; a diuretic) or

nitrendipine (a calcium blocker); 2) secondary: atenolol (generic; a beta-blocker); enalapril (generic; an ACE inhibitor); or captopril (generic; an ACE inhibitor).

Systolic BP was reduced to a mean of about 147. (*Note, not below 140.*)

Absolute reduction in risk of stroke over 5 years ranged from 1.4% to 3%. [NNT (5 years to benefit one) = 17 to 33]

Risk of other cardiovascular events was also reduced.

What is the evidence that BP reduction of patients with systolic 140-159 and diastolic less than 90 is beneficial?

To date, no large clinical trial has been performed in patient with stage one ISH. Most cases of "uncontrolled hypertension" in the USA are in fact stage one ISH. The evidence to support treatment of these patients to the level of 140 (and below) is not strong.

“Clarification of the benefit of treatment in these patients is therefore critical.”

The guidance for treatment comes primarily from observational data which document increased risks in patients with stage one ISH. The Framingham study reported a greater risk of development of cardiovascular disease; coronary heart disease; stroke; and heart failure in these patients (RRs = 1.47; 1.40; 1.42; and 1.60) compared with normotensive patients. (*The implication is that treatment would then be reasonable and that lowering systolic BP would reduce risks. RTJ*)

Should “white coat” hypertension be treated?

Whether elevated BP in the office and normal BP at home should be treated has been controversial.

“Informed patient preference and tolerance of therapy should guide treatment decisions for these patients.”

(*I would not treat an elderly patient with WCH. RTJ*)

What is the management approach for older patients with hypertension?

No long-term trials have been designed to assess the impact of life-style interventions on morbidity and mortality. Cardiovascular risk factors often cluster. Hypertensive patients tend to have increased prevalence of dyslipidemia, and insulin resistance. Overall cardiovascular risk should be considered: weight control, limited alcohol intake, limited sodium intake, increased physical activity and adequate potassium intake are recommended.

Medications:

Thiazide diuretics are an appealing option of for first-line therapy. Long-acting CCBs are also a reasonable first-choice for treatment of ISH.

A meta-analysis reported that diuretic therapy was superior to beta-blockade “Beta-blockers should therefore *not* be viewed as appropriate *first-line* therapy for uncomplicated ISH in the elderly patient.”

Many patients with ISH require more than one drug. Combination therapy is needed early in the treatment course. In selecting the 2nd drug, it is important to select a drug with a mechanism of action complementary to the first. Beta-blockers and ACE inhibitors both act by blocking renin release. There is less additive effect from using them together. There is also little to gain from adding a dihydropyridine CCB^a to a thiazide diuretic. Reasonable evidence-based combinations might be a 1) a diuretic + an ACE inhibitor^b, or 2) an ACE inhibitor + a CCB.

(**a** *There are 10 CCBs available. Two, diltiazem and verapamil, are the chief non-dihydropyridines.*)

(**b** *Why not hydrochlorothiazide and a generic beta-blocker? They are inexpensive. Dosage is easily adjusted.*)

What is the evidence or treating the oldest old (over age 85)?

In one trial, the benefit of active treatment compared with placebo reached its maximum at age 80. The RR for stroke in the oldest age group was 0.53 vs 0.74 in those age 60-69. “Evidence suggests that older patients do

benefit from treatment.” Clinicians should not withhold therapy solely according to advanced age. This group has an especially high risk of cardiovascular events. Individual patient preference and tolerance to therapy should be considered.

How can treatment decisions in older persons with ISH be optimized?

JNC 7 states that a BP higher than 140/90 warrants drug therapy, irrespective of age. But— “No randomized clinical trial evidence is available to demonstrate that reducing a BP of 140 to 159 (*to below 140 or below 130*) in older persons reduces morbidity or mortality.”

Hypertension treatment decisions in older persons must rely on extrapolations. They fall into a gray area in which the optimal choice for an individual may not be clear. The Institute of Medicine has supported the primacy of patient-centered care. This includes consideration of the older patient’s environmental, social, and cultural contexts to arrive at a shared decision about therapy.

Conclusion:

There is strong evidence of benefit to guide treatment of ISH at a systolic BP of 160 and above. Long term therapy reduces cardiovascular events and therapy should be advocated.

The evidence behind the JNC 7 guidelines about treatment of older patients with systolic BP 140-159 is less strong. No large scale studies have been performed to assess the effectiveness of treatment to lower BP below 140 in patient with isolated systolic BP 140-159. “Although JNC 7 states that patients should be treated to targets of less than 140 in most cases, and less than 130 if they have diabetes or chronic renal disease, there are no clinical trial data to support this recommendation.”

Evidence of treatment of ISH among the oldest old is also less strong.

However, treatment should not be withheld solely according to advanced age as this group has especially high cardiovascular risk. Therapy should be determined by balancing potential benefits of treatment with individual patient preference and tolerance to therapy.

There are risks to treatment-induced widened pulse pressure, especially if diastolic BP decreases to less than 60. Data suggests that thiazide diuretics are more effective in reducing pulse pressure than calcium blockers or ACE inhibitors. Older patients who used diuretics alone, or in combination with beta-blockers, had lower (more favorable) pulse pressures than patients using beta-blockers alone.

JAMA September 1, 2004; 292: 1074-80 “Clinical Review”, first author Sarwat J Chaudhry, West Haven Veterans Affairs Medical Center, West Haven, Conn.

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Few Patients Who Restrict Their Medication Use Because of Cost Appeared to Be Receiving Assistance from Their Health Care Providers.

9-2 COST-RELATED MEDICATION UNDERUSE

Patients often restrict their use of prescribed medications because of cost. Those who have chronic conditions, and require long-term medication are most vulnerable.

Underuse has been associated with serious health consequences, increased emergency department visits and nursing home admissions, and decrements in self-reported health status.

This nationwide survey identified a group of patients with chronic illnesses who reported underuse of medication and the reasons for underuse, mostly due to costs.

Conclusion: About 1/3 chronically ill adults who underused prescription medications because of costs never discussed this problem with their doctors.

STUDY

1. A nationwide survey identified over 600 older adults with chronic illnesses who reported underusing medication because of cost.
2. Assessed whether the patient discussed the problem with the doctor, the reasons given for the lack of communication, and how clinicians responded if the issue was raised.

RESULTS

1. The majority of these patients never told their doctor in advance that they planned to underuse the prescribed drug. About one third never brought up the issue at all.
2. Of those who did not tell the physician, about two thirds reported that nobody asked them about their ability to pay for the drug.
3. A majority reported that they did not think the doctor could help them. Some were too embarrassed to discuss the problem.
4. When patients did talk about the costs, the majority found the conversation helpful. However, many stated their prescription was never changed to a generic or to a less expensive alternative. They received no information about which drug(s) might be less necessary and might be excluded.
5. Few patients were given other forms of assistance such as referral to a social service agency, information about programs that help pay drug costs, or where to purchase less expensive medication.

DISCUSSION

1. Most chronically ill older patients who restricted their use of prescribed drugs because of costs did not tell the doctor about the problem. Most patients were never asked about cost problems.
2. Patients who were not asked by providers about the problem received a more negative message regarding the clinician's interest and potential ability to help them.
3. Most who did discuss the problem reported they were given free medication samples.^a
4. "Very few chronically ill patients who restrict their medication use because of cost appeared to be receiving assistance from their health care providers."

5. An interesting point: Some patients who had moderate to high incomes and therefore may have been financially capable of paying did not follow the prescription. They may have chosen to cut back on use because they placed little value on their medication relative to other potential purchases. This emphasizes the importance of patient education about the purpose of the drug, and the potential consequences of underuse.
6. Patients would appreciate information from their clinicians about financial assistance programs.
7. Some of the problem may have resulted from low functional health literacy.

CONCLUSION

Two thirds of chronically ill older patients who restricted their use of prescription drugs because of a cost problem did not tell their clinician in advance. Only one third ever raised the issue at all.

“Clinicians should take a more proactive role in identifying and assisting patients who have problems paying for prescription drugs.”

Archives Int Med September 13, 2004; 164: 1749-55 Original investigation, first author John D Piette, University of Michigan, Ann Arbor.

a The investigators discussed the pros and cons of free samples:

Free samples may actually *increase* patients out-of-pocket over the long-term. (Ie, if the specific drug is perceived as beneficial patients will likely wish to continue it.) Drug companies are fully aware of this and spend millions of dollars giving physicians free samples to dispense. “Free samples represent more than \$6.6 billion of the \$12.7 billion cost of drug promotion in United States. They can inflate retail costs for prescription drugs and lead providers to prescribe more expensive regimens.” Samples may exacerbate, rather than ameliorate the cost problem. A small short-term benefit may turn into a long-term expense.

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The Relationship Was Apparent in Persons Without Known Diabetes.

9-3 ASSOCIATION OF HEMOGLOBIN A1C WITH CARDIOVASCULAR DISEASE AND MORTALITY IN ADULTS

The present diagnostic thresholds of fasting plasma glucose [**fasting PG**] and 2-hour post challenge PG (**2-h PG**) are based on the relation between PG levels and *micro*-vascular complications of diabetes (retinopathy, nephropathy, and neuropathy).

Diabetes also raises the risk of *macro*-vascular disease. In contrast to micro-disease, increasing evidence suggests that the relation between PG and macro-disease (cardiovascular disease; **CVD**) is continuous and does not have obvious thresholds.

This study examined the relationship between HbA1c, coronary heart disease (**CHD**), cardiovascular disease (**CVD**) events, and total mortality.

Conclusion: The risk of CVD, CHD and mortality increased continuously as HbA1c rose. This included individuals *without* diabetes.

STUDY

1. A prospective population study followed over 10 000 men and women between ages 45-79 (mean = 62). Only 343 of the entire cohort had known diabetes.
2. Determined association between HbA1c (measured only once) and risk of cardiovascular disease events during a follow-up period (mean of 6 years).

RESULTS

1. During follow-up, 806 cardiovascular disease events and 521 deaths occurred.
2. The relationship between rising HbA1c levels and CVD events and deaths was continuous and significant throughout the whole distribution.
3. Cardiovascular disease events increased continuously from 6.7 per 100 men with HbA1c less than 5% to 35 per 100 men with HbA1c over 7%. Each increase of HbA1c of 1% was associated with a relative risk of 1.26 for death from any cause. A continuous increase was also noted in women, although at lower absolute numbers.
4. The relationship was apparent in persons without known diabetes.
5. Individuals with a HbA1c less than 5% had the lowest rates.
6. The relationship was independent of age, body mass index, waist circumference, systolic BP, serum cholesterol, smoking, and history of cardiovascular disease. (I.e, HbA1c may be an important independent risk factor.)

DISCUSSION

1. HbA1c levels were significantly associated with all-cause mortality and coronary and cardiovascular disease even below the threshold commonly accepted for the diagnosis of diabetes. In men, the risk for CHD was significantly increased in those with HbA1c 5.0% to 5.4% compared with those with HbA1c concentrations less than 5%.
2. Each increase of HbA1c of 1% was associated with a 20% to 30% increase in mortality and cardiovascular events. The gradient was apparent through the population range from less than 5% up to 6.9%.
3. Persons with HbA1c less than 5% made up one quarter of the sample. They had the lowest rates of mortality and CVD. Those with HbA1c over 7% made up 4% of the sample and contributed about 25% of the excess mortality.
4. The continuous relationship between HbA1c and CVD and mortality was evident even among persons without diabetes. Improvements in glycemic control might improve health outcomes among persons *without* diabetes.
5. Debate continues about which measure of glucose (fasting, 2-h post challenge, or HbA1c) is best to predict *macro*-vascular events. The Framingham study reported that all 3 factors are significant predictors. However, the 2-hour post-challenge PG was the measure that remained independently predictive of cardiovascular disease.
6. The authors state that the study could not rule out residual confounding and other known and unknown risk factors. Causality cannot be determined from observations studies.

CONCLUSION

The risk of CVD and mortality increased continuously as HbA1c rose. Most events occurred in persons with moderately elevated HbA1c. Reduction in HbA1c levels in persons *without* diabetes may lessen their risk.

Annals Int Med September 21, 2004; 141: 413-20 Original investigation by the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) study, first author Kay-Tee Khaw, University of Cambridge School of Clinical Medicine, UK.

See also: *Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus*, a companion article in this issue of Annals (pp 421-31) first author Elizabeth Selvin, Johns Hopkins Bloomberg School of Public Health, Baltimore MD. It reports a meta-analysis of observational studies comparing risks of *macro*-vascular disease (CVD) with HbA1c levels in patients with diabetes. The analysis suggests that chronic hyperglycemia is associated with increased risk of CVD.

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HbA1c is an Independent and Progressive Risk Factor for Incident CVD Regardless of Diabetes Status.

9-4 GLYCOSYLATED HEMOGLOBIN: FINALLY READY FOR PRIME TIME AS A CARDIOVASCULAR RISK FACTOR.

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

The societal burden of the diabetic epidemic is being fueled by our current lifestyle. Diabetes is just the measured tip of a much larger “dysglycemic iceberg”. Diabetes is diagnosed when the fasting plasma glucose (PG) is consistently 126 mg/dL or over, or when the 2-hour post-challenge (75-g glucose load) PG is 200 or greater. These thresholds are much greater than “normal” fasting and 2-h mean levels.^a

These levels were chosen because they effectively differentiate individuals at high risk of diabetic eye disease from individuals at low risk. They were not chosen based on risk of cardiovascular disease (CVD).

It is now clear that fasting and 2-h PG levels well below the diabetes cutoffs are cardiovascular risk factors. And that a progressive relationship between PG and CVD risks extends from normal glucose levels right into the diabetic range, with no clear lower threshold.

Glycosylated hemoglobin is an easily measured marker that strongly correlates with the level of ambient glycemia during a 2- to 3-month period. (HbA1c is a specific sub-type of glycosylated hemoglobin.) It reflects the usual daily fasting and postprandial glucose levels. It is strongly linked to micro-vascular disease in patients with diabetes. The test is inexpensive and can be done at any time of day.

One meta-analysis reported that, in patients with type 2 diabetes, a 1% rise in HbA1c was associated with a significant 18% increase in risk of CHD and stroke, and a 28% rise in risk of peripheral vascular disease. Measures which decrease HbA1c reduce the risk of eye, kidney, and nerve disease in persons with type 1 and type 2 diabetes

Now, evidence is accumulating that HbA1c is a progressive risk factor for CVD in people *without* diabetes as well as people with diabetes. Every 1% point absolute increase above a clearly normoglycemic level predicts a 20% relative increase in the incidence of cardiovascular events. “The glycosylated hemoglobin level can now be

added to the list of other clearly established indicators of cardiovascular risk such as blood pressure and cholesterol level.”

We can conclude that HbA1c is an independent and progressive risk factor for incident CVD regardless of diabetes status. “Glycosylated hemoglobin level can now be added to the list of other clearly established indicators of CVD risk.”

“The presence or absence of diabetes is likely to become less important than the level of glycosylated hemoglobin in the assessment of cardiovascular risk.”

A very small shift in the general population’s average HbA1c of 0.2% could dramatically affect the future incidence of CVD.

Annals Int Med September 21, 2004; 141: 475-76 Editorial by Hertz G Gerstein, McMaster University, Hamilton, Ontario, Canada.

a The editorialist stated the mean normal fasting PG is 92 mg/dL. And the mean normal 2-h post glucose load PG is 97 mg/dL

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Associated With More Than A 50% Lower Rate Of Death

9-5 MEDITERRANEAN DIET, LIFESTYLE FACTORS, AND 10-YEAR MORTALITY IN ELDERLY EUROPEAN MEN AND WOMEN

“Regardless of predisposing factors, diet and lifestyle influence morbidity and mortality during the course of life.” Because of the cumulative effect of adverse factors throughout life, it is particularly important for older persons to adopt diet and lifestyle practices that minimize their risk of death and morbidity and maximize their prospects for healthful aging.

This study investigated the association of dietary patterns and lifestyle factors with mortality in elderly men and women in 11 European countries.

Conclusion: Among individuals aged 70-90, adherence to a Mediterranean diet (**MD**) and a healthy lifestyle was associated with more than 50% lower rate of death over 10 years.

STUDY

1. Followed a cohort of over 1500 apparently healthy men and over 800 apparently healthy women age 70-90 (mean = 75) at baseline.
2. Investigated the single and combined effect of 4 factors (Mediterranean diet, being physically active, moderate alcohol use, and non-smoking) on mortality.
3. A Mediterranean diet score was based on 8 components: ratio of mono-unsaturated to saturated fat; legumes, nuts, and seeds; grains; fruit; vegetables and potatoes; meat and meat products; dairy products; and fish. The diet score ranged from 0 (low-quality) to 8 (high quality).
4. Main outcome measures = 10-year mortality from coronary heart disease (**CHD**), cardiovascular disease (**CVD**), cancer, and all causes

RESULTS

1. During the follow-up of 10 years 935 participants died.
2. Each of the 4 factors was individually associated with lower mortality rates from CHD, CVD, cancer, and all causes.

	Hazard ratio of death
MD (4 or more points)	0.77
Moderate alcohol use	0.78
Physical activity	0.63
Non-smoking	0.65
3. Individuals with 2, 3, or 4 low-risk factors had a significantly lower mortality compared with individuals with 0 or 1 low-risk factors.

	Hazard Ratios:			
No. of protective factors:	0-1	2	3	4
CHD mortality	1.00	0.50	0.43	0.27
CVD mortality	1.00	0.60	0.44	0.33
Cancer mortality	1.00	0.65	0.42	0.31
All cause mortality	1.00	0.62	0.45	0.35
5. A lack of adherence to the low-risk pattern was associated with a population-attributable risk of about 60% of all deaths.
6. The combination of all 4 low-risk factors reduced the relative risk of all-cause mortality rate to 0.35

DISCUSSION

1. During a 10-year follow-up, individuals between 70 and 90 years who had adhered to a MD, were non-smokers, were physically active, and used alcohol moderately had less than half to mortality from all causes, CHD, CVD, and cancer than those who did not adhere to the factors.
2. The investigators considered that diet and lifestyle were stable in these older individuals.

CONCLUSION

Among individuals age 70 to 90, adherence to a MD and healthful lifestyles was associated with a more than 50% lower risk of mortality over 10 years.

JAMA September 22/29, 2004; 292: 1433-39 Original investigation by The Healthy Ageing: a Longitudinal study in Europe population (HALE) study, first author Kim T B Knops, Wageningen University, the Netherlands

A randomized trial reported in this issue of JAMA (pp 1440-46) *Effect of a Mediterranean-style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome*, from Universita di Napoli, Naples, Italy, first author Katherine Esposito, reported that adherence to a Mediterranean diet might be effective in reducing prevalence of the metabolic syndrome and its associated cardiovascular risk.

“There Is A Biology of Frailty That May Be Independent of Age and Specific Disease States.”

Far Out . . . But Provocative

9-6 FRAILITY—AND ITS DANGEROUS EFFECTS—MIGHT BE PREVENTABLE.

The differences between a 70-year-old who is robust and one who is frail are easily detectable. Frail old people are more vulnerable, withdrawn, unsteady, and weak. “In short, doctors know frailty when they see it.”

Until recently, diagnosing frailty was mostly subjective. Physicians seldom thought of specific treatment. Now there is an objective method for diagnosis. This opens the door to potential treatment. The newer view moves away from the common view that frailty is an inevitable part of old age toward a new view of frailty as an avoidable condition.

Whether frailty is a disease or a set of related medical disorders is not clear. Some experts believe that frailty may some day be an official coded disease, replete with FDA-approved treatments. It is likely that the diagnosis will be based on both laboratory tests and physical findings. Increases in markers of inflammation and blood clotting activity have been described. Treatments may target hormonal and inflammatory pathways.

A recent study defined frailty as having at least 3 of 5 attributes: unintentional weight loss; muscle weakness; slow walking speed; exhaustion; and low physical activity.^a These findings persist in some old persons despite exclusion of the most common chronic illnesses. About 7% of persons older than 65, and 20% of those over age 80 may fit the definition of frailty. A screening tool for frailty has been described—gait speed, chair stands, and tandem balance. *(It should also include a test for mental agility. RTJ)*

“There is a biology of frailty that may be independent of age and specific disease states.” But just what triggers frailty in some individuals and not others is not clear. “The concept to maintaining and regaining homeostasis is a key factor in warding off the vicious cycle of frailty.” Perhaps the most obvious treatment for stopping frailty (but not the only treatment) is physical exercise. One home-based physical therapy study reported a slowing of functional decline in frail persons. However, there is no evidence that late-life exercise reduces disability.^b

“If you can identify frailty, you can work back to understanding its pathophysiology, and possibly identify factors that we haven’t appreciated before.”

Annals Int Med September 21, 2004; 141: 489-90 , “Current Clinical Issues”, commentary by Jennifer Fisher Wilson, Science reporter, Annals of Internal Medicine.

a The five attributes would require a definition of the degree of the decline. Certainly, factors in addition to the five affect frailty. (Eg, Alzheimer’s disease.)

b Don’t wait until it is too late. See preceding articles on extension of a productive and enjoyable life-span by a healthful life-style before frailty and” old-age” set in. RTJ

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The Great Majority of Patients Actually Had Migraine.

9-7 PREVALENCE OF MIGRAINE IN PATIENTS WITH A HISTORY OF SELF-REPORTED OR PHYSICIAN-DIAGNOSED “SINUS” HEADACHE.

The ability of clinicians to help sufferers to achieve meaningful control of acute episodes of migraine has increased substantially. New effective treatment options are available. Clinicians now better understand how to manage migraine.

Despite this, an estimated half of migraine sufferers are not diagnosed. Among the factors contributing to under recognition is the variability of clinical presentation of the headache. **(HA)** Migraine may be accompanied by symptoms commonly associated with other types of headache. This confuses attempts at diagnosis.

“Sinus” headache may constitute one of the most common and misdiagnosed clinical presentations of migraine. Symptoms referable to the sinus areas are frequently reported during migraine attacks. They are not recognized as diagnostic criteria for migraine.

This study determined the presence of migraine-type headache (defined by the International Headache Society **(IHS)** classification of migraine) in patients with “sinus” headaches. The IHS states that chronic sinusitis is *not* validated as a cause of HA or facial pain unless it relapses into an acute phase.

Conclusion: The great majority of patients with a history of “sinus” HA were determined to have migraine-type HA. The presence to sinus-area symptoms may be a part of the migraine process. Overdiagnosis of “sinus” HA contributes to under-recognition of migraine. And undertreatment.

STUDY

1. Entered a clinic-based sample of patients (n ~ 3000) age 18 to 65. Most of the patients were white women mean age 39. All had a history of “sinus” HA, either self-diagnosed or diagnosed by a physician. None had a previous diagnosis of migraine or used triptan drugs. None had evidence of sinus infection (fever, radiographic evidence of sinus infection, or purulent discharge).
2. All had experienced at least 6 self-described, or physician-diagnosed “sinus” HA during the previous 6 months. The subjects reported a mean of 3 HA per month. The impact of the HA on health-related quality-of-life was severe.

RESULTS

1. Sinus pressure, sinus pain, and nasal congestion were the most common symptoms referable to the sinus area.
2. Eighty-eight % of the patients were diagnosed at screening as fulfilling the IHS migraine criteria: (migraine (80% of patients) or migrainous disorder criteria (8%).
3. Most patients reported characteristics of typical migraine: worsening pain with physical activity, nausea, pulsating/throbbing pain, phonophobia, and photophobia. Most also reported sinus pressure, sinus pain, and nasal congestion.
4. The majority expressed some dissatisfaction with the medication they used to treat their HA. (Mainly non-narcotic analgesics, NSAIDs, decongestants, and antihistamines.)

DISCUSSION

1. The results of this primary-care clinic-based study, show that patients with a history of self-described or physician-diagnosed “sinus” headache and no previous diagnosis of migraine commonly met IHS criteria for migraine or migrainous headache.
2. Patients and physicians commonly label migraine attacks that have “sinus” features as sinus headaches.
3. Although most patients reported typical migraine symptoms, the majority also reported nasal and ocular symptoms.
4. “Sinus” HA is one of the most commonly reported terms used by undiagnosed migraineurs to identify their headaches. The tendency to conceptualize nasal and ocular symptoms as being uncharacteristic of migraine may be attributed in part to IHS criteria, which does not list these symptoms as criteria for assigning a diagnosis of migraine. The criteria notwithstanding, experts note the frequent occurrence of nasal and ocular symptoms in migraine (unilateral runny nose, lacrimation, conjunctival injection, and nasal congestion). Patients may conceptualize these symptoms as “sinus”. Advertisements of over-the-counter sinus medications have repeatedly conveyed that pounding pain is associated with “sinus” headaches.
5. In clinical practice, recognizing that patients with episodic headaches in which nasal and sinus symptoms predominate actually suffer from migraine is crucially important because accurate diagnose determines the appropriate course of treatment. In these patients, especially those reporting very severe headaches, migraine-specific therapy may relieve pain and restore functional ability. Antihistamines and decongestants do not relieve this pain.
6. The IHS diagnostic criteria for acute sinus HA include purulent discharge, pathological sinus findings on imaging, simultaneous onset of HA and sinusitis, and HA localized to specific facial and cranial areas near the sinuses. All 4 criteria are needed to make the diagnosis. Allergists and neurologists contend that “sinus” HA is rare even among patients with sinus infection. One must question—what is “sinus” headache, especially in the absence of infection?

CONCLUSION

The great majority of patients with a self- or physician-diagnosed “sinus” HA actually had migraine. The presence of sinus-area symptoms may be part of the migraine process.

Archives Int Med September 13, 2004; 164: 1769-72 Original investigation, first author Curtis P Schreiber, Headache Care Center, Springfield MO.

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Associated with Significantly Better Cognitive Function and Less Cognitive Decline in Older Women.

9-8 PHYSICAL ACTIVITY, INCLUDING WALKING, AND COGNITIVE FUNCTION IN OLDER WOMEN

Some evidence suggests that physical activity may reduce the risk of cognitive decline. What intensity of activity is required?

This study examined the relation of long-term regular physical activity, including walking, to cognitive function in a large cohort of women.

Conclusion: Long-term physical activity, including walking, was associated with better cognitive function.

STUDY

1. This subset of The Nurse Health Study included over 18 000 women age 70-81 (mean 74) at baseline (1986).
2. Determined leisure-time physical activity by questionnaire every 2 years.
3. Assessed cognitive performance and cognitive decline over 2-year periods (1995 to 2000). Cognition was assessed by tests for general cognition, verbal memory, fluency, and attention.
4. Calculated cut points (quintiles) for expenditure of energy in walking, beginning at a pace of 20-30 minutes per mile for less than 38 minutes per week up to more than 2.8 hours per week. (Ie, about 30 minutes daily.)
5. Estimated adjusted mean differences in energy expenditures related to cognitive decline.

RESULTS

1. Higher levels of activity were associated with better cognitive performance.
2. On a global score combining results of all cognitive tests, women in the second through the fifth quintile of energy expenditures scored an average of 0.06, 0.06, 0.09, and 0.1 standard units higher than women in the lowest quintile.
3. Compared with women in the lowest physical activity quintile, those in the highest quintile had a 20% lower risk of cognitive impairment.
4. Among women performing the equivalent of walking at an easy pace for at least 1.5 hours per week, mean global scores were 0.06 units higher compared with walking less than 40 minutes per week.

DISCUSSION

1. "In this large prospective study of older women, higher levels of long-term regular physical activity were strongly associated with higher levels of cognitive function and less cognitive decline. This benefit was similar in extent to being about 3 years younger in age."
2. The association was not restricted to women engaging in vigorous activity. Walking the equivalent of at least 1.5 hours per week at a 20 to 30 minute per mile pace was also associated with better cognitive performance.
3. The study did not consider dementia. However, previous studies have reported that poorer cognitive function is related to subsequent development of dementia.
4. Mechanisms for the association may include benefit of physical activity on the brain's vascular health by lowering BP, improving lipid profiles, improving endothelial function, and ensuring adequate cerebral perfusion.
5. Four other large-scale prospective studies have also reported that greater physical activity benefits cognitive function.

CONCLUSION

Long-term regular physical activity, including walking, was associated with significantly better cognitive function and less cognitive decline in older women.

JAMA September 22/29, 2004; 292: 1454-61 Original investigation, first author Jennifer Weuve, Harvard School of Public Health, Boston, Mass.

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Patients with IBS Demonstrate an Altered Response to Stress and Inadequate Psychological Adaptation

9-9 CLINICAL DETERMINANTS OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME.

Irritable bowel syndrome (**IBS**) is a chronic disorder of gastrointestinal function characterized by recurrent abdominal pain and altered bowel function in the absence of any detectable organic disease.

Patients with IBS have a health-related quality of life (**HRQOL**) that may be significantly worse than some other chronic diseases such as diabetes and end-stage kidney disease.

This study identified a concise and readily available set of mental and physical factors in patients with IBS that might lead to physician's gaining better insight into these patients. HRQOL in patients with IBS may be related to extraintestinal symptoms that physicians neglect to ask about.

Conclusion: HRQOL in patients with IBS is primarily related to extra-intestinal symptoms.

STUDY

1. Examined 770 patients with IBS. All completed symptom questionnaires: the SF-30 and the Symptoms Checklist-90-items psychometric checklist.
2. The investigators then analyzed the independent association of each predictor to arrive at a short list of factors related to HRQOL.

RESULTS

1. Seven factors independently predicted *physical* HRQOL: 1) more than 5 physician visits per year; 2) tiring easily; 3) low in energy; 4) severe symptoms; 5) predominantly pain symptoms; 6) feeling that there is something seriously wrong with body; 7) symptom flares longer than 24 hours.
2. Other factors independently predicted *mental* HRQOL: 1) feeling tense; 2) feeling nervous; 3) feeling hopeless; 4) difficulty sleeping; 5) tiring easily; 6) low sexual interest; 7) IBS symptoms interfere with sexual interest.

DISCUSSION

1. Patient-perceived health not only defines their condition, but also serves as a primary outcome to measure the impact of therapy. An important goal of the patient-physician interaction is to accurately assess HRQOL. Addressing HRQOL allows clinicians to better understand patient needs, modify care-seeking patterns, and improve adherence to therapy.

2. Both the physical and mental domains of the assessment of HRQOL share a strong association with symptoms of chronic stress and exhaustion (eg, tire easily, low energy, low sexual drive, and sleep difficulties). Neither is determined by the presence of specific gastrointestinal symptoms, the degree of previous gastrointestinal evaluation, or any demographic characteristic.
3. Healthy persons maintain homeostasis in the face of stress through precisely timed coordination of adaptive biologic response systems. Patients with IBS demonstrate an altered response to stress and inadequate psychological adaptation over time.
4. Chronic stress-system activation in patients with IBS may manifest with exaggerated autonomic, neuroendocrine, or pain modulation responses that lead to long-term altered bowel function and visceral perception.
5. Symptoms of exhaustion are highly significant determinants of HRQOL in patients with IBS.
6. Instead of focusing on physiological epiphenomena (stool frequency, stool characteristics, and subtype of IBS), physicians might better serve the patient by gauging *global* symptom severity, addressing anxiety, and identifying and eliminating factors contributing to chronic stress.
7. By screening for predictors of HRQOL, physicians may be in a position to initiate effective, timely, and self-empowering therapy, to teach coping mechanisms and relaxation skills, to promote appropriate life-style modifications and allow patients to recognize their own limitations.
8. Recent data indicate that directed psychotherapy is effective and cost-effective in management of IBS.

CONCLUSION

HRQOL in patients with IBS is primarily lowered by *extraintestinal* symptoms rather than traditional gastrointestinal symptoms. Patients might be better served if their physician gauges global symptoms, addresses anxiety, and helps to eliminate factors contributing to chronic stress.

Archives Int Med September 13, 2004; 164: 1773-80 Original investigation, first author Brennan M R Spiegel, David Geffen School of Medicine at UCLA, Los Angeles, CA.
