PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

A FREE PUBLIC SERVICE PUBLICATION

ABSTRACTED MONTHLY FROM THE JOURNALS

DECEMBER 2008

THE CHALLENGE OF PREVENTIVE TREATMENT [12-1]

THE CLINICAL EQUIVALENCE OF GENERIC AND BRAND-NAME DRUGS [12-2]

TREATMENT OF IRRITABLE BOWEL SYNDROME IN PRIMARY CARE [12-3]

LOW SOCIOECONOMIC STATUS—A MAJOR RISK FACTOR FOR CHD [12-4]

ROUTINE SCREENING FOR DEPRESSION IN PATIENTS WITH CHD. [12-5]

ORAL HEALTH AND SYSTEMIC DISEASE [12-6]

PSA SCREENING FOR PROSTATE CANCER IN MEN OVER AGE 75 [12-7]

EFFECT OF A LOW-GLYCEMIC DIET ON TYPE- DIABETES [12-8]

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

To request monthly issues go to Rjames6556@aol.com

This document is divided into two parts

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

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

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

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

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

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

Practical Pointers is published every month on the internet as a public service. It is available on a more timely basis by e-mail attachment. It contains no advertising. It is completely without bias. There is never any charge.

Requests for "subscription" to rjames6556@aol.com

HIGHLIGHTS AND *EDITORIAL COMMENTS* DECEMBER 2008

Clinicians Face Challenges In Applying Preventive Interventions.

12-1 IS CLINICAL PREVENTION BETTER THAN CURE?

In wealthy countries, the focus of clinical care is changing from cure to prevention—to anticipate future disease in currently healthy persons. Prevention has an aura of omnipotence and good sense. Is it always true that prevention is better than cure?

This essay reviews challenges clinicians face in applying preventive interventions.

New thinking is needed about the benefits and potential harms of prevention in clinical medicine. Prevention can cause harm. Potential harms include increased fear and perception of illness when none exists; assuming that prevention is of equal value for everyone; and frustration on the part of clinicians over a growing list of requirements that are impossible to accommodate within the clinical visit.

Many preventive interventions are promoted without sufficient evidence of benefits, cost effectiveness, and feasibility in routine clinical visits.

Prevention can be complex and expensive. Clinicians may find it difficult to carry out the recommended strategies. Labeling almost always heightens anxiety and may lead to other tests and consultations. Drugs, which patients must take for the rest of their lives (a particular concern for young patients with mild hypertension) do not guarantee individual benefit.

Not all preventive activities have the same benefit, adverse effect profile, and costs. Judgment is required in adhering to recommendations, taking into account different biological, cultural, social, and economic contexts, patient's preferences, the natural history of the disease, co-occurring risks, relative, attributable, and absolute risk, and prevalence in the population.

Primary care clinicians should consider:

The harms of labeling and the adverse effects of preventive interventions may be high.

Life-style recommendations first. They are associated with low risk. (Also low compliance.)

Intervention should be based on negotiation with an informed patient. (This may be difficult and take time.)

It is difficult for patients to initiate preventive measures and to continue them (eg, seat belts, condoms), Compliance after initial enthusiasm will lag.

Development of the "medical home" potentially will improve application of preventive interventions. One member of the team may assume the responsibility to follow-up, contacting patients periodically to ask if they are complying.

"Similar In Nearly All Clinical Outcomes."

12-2 CLINICAL EQUIVALENCE OF GENERIC AND BRAND-NAME DRUGS USED IN CARDIOVASCULAR DISEASE *A Systematic Review and Meta-analysis*

Generics are chemically equivalent to their brand-name counterparts in terms of active ingredients. They may differ in specific manufacturing processes. The FDA requires generics to be "biologically equivalent"—defined as absence of a significant difference in the availability of the active ingredients at the site of drug action. Bioequivalence can be established on the basis of the maximum serum concentration of the drug, the time until maximum concentration is reached, or the area under the curve based on serum concentration as a function of time.

There has been concern that "bioequivalent" generic and brand-name drugs may not be equivalent in their effects on various cardiovascular disease clinical parameters including physiological measures (eg, heart rate and BP), laboratory measurements, and outcomes. Of particular concern are drugs with a narrow therapeutic index (effective dose and toxic dose are separated by a small difference in plasma concentration (eg, warfarin; antiarrhythmic drugs). Anecdotes have appeared in the lay press raising doubts about efficacy and safety of certain generics. Are generics inferior to brand-names?

This study evaluated comparisons of generics and brand-name drugs on these outcomes.

Wide therapeutic index (WTI) drugs:

Considered 7 different drug classes (mainly beta-blockers, diuretics, and calcium blockers).

Clinical equivalence was noted in randomized, controlled trials (RCTs) of:

- 7 of 7 beta-blockers
- 10 of 11 diuretics
- 5 of 7 calcium blockers
- 3 of 3 antiplatelet agents
- 2 of 2 of statins
- 1 of 1 ACE inhibitors
- 1 of 1 alpha blockers.

Narrow therapeutic index (NTI) drugs:

Clinical equivalence was noted in RCTs of:

- 1 of 1 class I antiarrhythmic agents
- 5 of 5 warfarin.

Among 43 editorials, 23 (53%) expressed a negative view of generic drug substitution; 12 (28%) encouraged substitution of a generic. Among NTI drugs, 12 expressed a negative view; 4 supported substitution.

Conclusion: Evidence does not support the notion that generic drugs used in cardiovascular disease are inferior to brand-name drugs. A substantial number of editorials, however, counsel against interchangeability of generic drugs with brand-name drugs.

Many pharmacies now offer a long list of generics (not all) for $4 for a month's supply ($10 for 3 months). This appreciably increases the benefit/harm-cost ratio of the drug. It will increase compliance and generalizability because many patients cannot afford costs of brand-name drugs. For example, my pharmacy charges $1.17 for 5 mg coumadin; about 10 cents for generic warfarin.

If plans were to prescribe a generic, would it not be advisable to start with the generic? And try to maintain the same manufacturer throughout the treatment period.

Regretfully, I have doubts about generics produced abroad, especially China. Make sure the FDA has rated the drug as bioequivalent. Is every batch of the drug checked for bio-equivalence? I would purchase the generic from a well-known pharmacy. I would not order by mail, or e-mail, especially from a foreign country.

Our primary care free clinic prescribes only generics. Anecdotally, patients do well.

Note that the authors of the article hedged a bit in their discussion. Please read the full abstract.

Psyllium, Hyoscine, and Peppermint Oil are Better than Placebo

12-3 TREATMENT OF IRRITABLE BOWEL SYNDROME IN PRIMARY CARE:

Irritable bowel syndrome (**IBS**) is common and difficult to treat. A wide range of treatments is used: dietary exclusion; fiber supplements; probiotics; antispasmodic drugs; antidiarrheal agents; laxatives; antidepressants;; hypnotherapy; and cognitive behavioral therapy.

A high placebo response has been observed. This highlights our ignorance about the cause of IBS.

A systematic review in this issue of BMJ summarizes the effect of three different agents: fiber, antispasmodic drugs, and peppermint oil.

The number needed to treat to benefit one patient:

Fiber	12	(12 trials)
Antispasmodics	5	(22 trials)
Peppermint oil	2.5	(4 trials)

(All were more effective than placebo.)

Peppermint oil (available without a prescription) seemed to be the most promising agent.

The meta-analysis lacked information on the subtype of IBS (constipation predominant, diarrhea predominant, or alternating), drug dosage, and patterns of administration. It provided no guidance on patient selection for a particular agent. This limits clinical applicability.

Treatment should be based on an individual trial-and-effect response. As the article states, we do not know the pathophysiology of IBS. Reasonably, the choice of the first agent would depend on the predominant symptom. The best approach might be to allow individual patients to choose a treatment option after being informed about the best of available studies. It would be reasonable to choose the least expensive OTC drug first. And then proceeding to a N = 1 trial.

"Risks Are Systematically Underestimated Among Persons With Lower SES"

12-4 SOCIOECONOMIC STATUS AND CORONARY HEART DISEASE PREDICTION

Disparity in life expectancy between groups of individuals with low social economic status (**SES**) and those with high SES has been increasing. Much of this disparity is attributable to higher mortality from coronary heart disease among persons with lower SES.

Disparities arise because of: early life environment; material disadvantage; social and behavioral risk factors; access to care; costs; and health literacy.

The risk of low SES for CHD is independent of age, sex, diabetes, physical activity, diet, cholesterol, and bodyweight.

A study from Scotland reported that the Framingham risk score (FRS) underpredicted risk of CHD among persons with low SES. Predicted by the FRS, individuals living in communities with the lowest income had a 3% higher estimated risk than those living in the wealthiest communities. Actually, the risk was 41% higher.

Primary care clinicians deal with individuals. How do we measure the SES of an individual?

I have followed the "Polypill" concept for years. The original recommendation was to give the pill to everyone over age 50. Limiting the pill to individuals with low SES might be more effective.

Screen Patients with CHD for Depression

12-5 ROUTINE DEPRESSION SCREENING ADVISED FOR PATIENT WITH CORONARY HEART DISEASE

Up to 20% of patients with myocardial infarction (**MI**) meet the criteria for major depression. Depression is not a "normal" occurrence after a MI.

The American Heart Association advises clinicians to regularly screen patients with CHD for depression. The American Psychiatric Association agrees.

Comorbidity of depression and CHD leads to worse outcomes for both conditions.

Treatment includes cognitive-behavior therapy and physical activity. SSRIs such as sertraline (Generic; *Zoloft*, Pfizer) and citalopram (Generic; *Celexa*, Forest) seem safe soon after an MI.

There is evidence that patients who do not get better from their depression are at high risk of dying.

The Health Of The Mouth Can Have Significant Effects On The Health Of The Rest Of The Body

12-6 ORAL HEALTH—DIABETES LINK

Poor oral health can have significant effects on the health of the rest of the body.

When bacteria from periodontal disease (**PD**) are released into the blood stream, production of pro-inflammatory cytokines increases. The body's response is systemic.

The link between PD and heart disease is one of the most commonly known associations.

Conditions within the oral cavity appear to have a particularly close relationship with diabetes. Poor oral health may have adverse effects on diabetes.

The relationship goes both ways. Diabetes can lead to adverse changes in oral health.

Although short and anecdotal, I believe this report calls attention to a relationship important to primary care.

Throughout the years, I paid scant attention to oral health of my patients. I assumed that it was entirely a dental problem.

"Think Twice, Or Even 3 Times."

12-7 SCREENING FOR PROSTATE CANCER AMONG MEN 75 YEARS OF AGE AND OLDER

Prostate cancer (**PC**) screening with prostate specific antigen (**PSA**) remains one of the most controversial issues in medicine.

The US Preventive Services Task Force (USPSTF) recently revised its recommendation regarding screening, concluding that "the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men *younger* than age 75 years".

Furthermore, it now "recommends *against* screening for prostate cancer in men age 75 years and older".

The new recommendations imply that clinicians should discuss the potential benefits and known harms of screening with men between age 50 and 74, but not necessarily with older men.

Why change the recommendations for men over age 75? The task force believes that at least a moderate amount of evidence now makes it possible to conclude that the known harms of screening outweigh the possible benefits in this age group. The risks of postoperative death and complications from radical prostatectomy are age related, escalating above age 75

The new advice is "do not bring up the subject of PSA screening for elderly patients". Indeed, ordering a PSA at any age without discussing the harms and benefits, and letting the informed- patient decide, is a mistake. Even after age 75, personal choice is important. I would not deny a PSA screen for an elderly man who insists upon it. But, only after a calm discussion of harms and benefits.

This is another good example of how fashions in medicine change. When first introduced, PSA was touted as a major advance.

Resulted In A Moderately Lower Hba1c Level.

12-8 EFFECT OF A LOW-GLYCEMIC INDEX OR A HIGH-CEREAL FIBER DIET ON TYPE 2 DIABETES

The relevance and practicality of applying the low-glycemic index diet (**L-GID**) to treatment of diabetes has been questioned. This randomized trial assessed the effect of a L-GID in patients with DM-2 treated with oral agents.

The trial entered 210 volunteer patients with DM-2 (mean age = 61). All were taking oral antidiabetes drugs (other than acarbose). The drugs were continued. HbA1c ranged between 6.5% and 8.0%. (Mean = 7.1%)

Randomized to: 1) L-GID, or 2) high-cereal fiber diet as a control. The diets were structured.

Mean outcomes: :	Baseline		6 months	
	High fiber	L-GID	High fiber	L-GID
HbA1c (%)	7.07	7.14	6.89 (-0.18%)	6.64 (-0.50%)
Fasting glucose (mg/dL)	141	139	137 (- 4)	128 (-11)
Body weight (kg)	87.8	87.0	86.2 (-1.8)	84.5 (-2.5)
High density cholesterol	43.1	41.9	42.8 (- 0.3)	43.6 (+1.7)

The change in HbA1c was modest, The investigators, however, believe it has clinical relevance.

The intervention was associated with weight loss. (Weight *gain* often accompanies treatment with glucose-lowering medications.)

These improvements were achieved in individuals who continued treatment with oral drugs.

Conclusion: Treatment of DM-2 for 6 months with a L-GID resulted in a moderately lower HbA1c level. L-GID may be useful as part of the strategy to improve glycemic control in patients with DM-2 who are taking antidiabetes drugs.

Every little bit helps.

I doubt, however, that many primary care patients would long abide with the diet. (Note that 20% of subjects in this enthusiastic trial dropped out.) It is easier to take another pill.

Patients can be advised that L-GID does help to improve control and reduce risk factors.

ABSTRACTS DECEMBER 2008

Clinicians Face Challenges In Applying Preventive Interventions.

12-1 IS CLINICAL PREVENTION BETTER THAN CURE?

In wealthy countries, the focus of clinical care is changing from cure to prevention—to anticipate future disease in currently healthy persons. Prevention has an aura of omnipotence and good sense. Is it always true that prevention is better than cure?

Clinical prevention, including immunizations and lifestyle advice, is an important and positive component of almost every clinical visit.

This essay reviews challenges clinicians face in applying preventive interventions.

Is identification of a risk factor always (or even generally) an indication for preventive activities?

New thinking is needed about the benefits and potential harms of prevention in clinical medicine.

Prevention can cause harm. Potential harms include increased fear and perception of illness when none exists; assuming that prevention is of equal value for everyone; and frustration on the part of clinicians over a growing list of requirements that is impossible to accommodate within the clinical visit.

Many preventive interventions are promoted without sufficient evidence of benefits, cost effectiveness, and feasibility in routine clinical visits. This article explores several specific challenges of preventive interventions, and suggests possible ways of tackling them.

For hypertension, evidence suggests that the benefits of screening and prevention substantially outweigh harms. Yet, prevention can be complex and expensive. Clinicians may find it difficult to carryout the recommended strategies. Labeling almost always heightens anxiety and may lead to other tests and consultations. Drugs, which patients must take for the rest of their lives (a particular concern for young patients) do not guarantee individual benefit.

Prevention needs more careful assessment than treatment. Prevention is presented as beneficial to people who are well. It is typically initiated by the doctor rather than by the patient. And it carries a real risk of causing harm.

The individual's current level of health should always be taken into account. Clinicians, in their attempt to do everything, may initiate multiple diagnostic and preventive activities, each leading to poorly recognized ill effects. Each added prevention, even if of high quality, increases the risk of adverse effects and drug interactions (especially in the elderly).

Prediction rules (eg, the Framingham risk score) are based on risk factors. Prediction rules have been equated with decision rules; population risk has been applied to individual risk, and risk is being applied to populations other than those for whom they were developed. Diseases have been recast on the basis of

often arbitrary laboratory values. “We turn people into patients without any evidence of benefit to them individually.”

The US Preventive Services Task Force (USPSTF) assesses single interventions for asymptomatic patients, but gives no indications as to how different interventions should be combined. Its recommendations are not intended for patients who have developed symptoms or signs of disease, or have comorbidity.

Not all preventive activities have the same benefit, adverse effect profile, and costs. Judgment is required in adhering to recommendations, taking into account different biological, cultural, social, and economic contexts, patient’s preferences, the natural history of the disease, co-occurring risks, relative, attributable, and absolute risk, and prevalence in the population.

Preventive and treatment interventions have different effects on life expectancy. Care of illness should not be compromised in favor of preventive activities. Care should receive priority from available resources (clinician’s time perhaps being the most important).

The authors propose principles to guide assessment of new recommendations for clinical prevention:

Evidence of benefits and feasibility must be tested in ordinary practice.

Not all preventive activities are of equal value.

Reduction of relative risk is not enough.

All trials on which policy is based should assess harms.

“Prevention interventions take from the poor and give to the rich. Insecure, impoverished, culturally disenfranchised, or alienated people are less likely to take part in preventive activities than people with greater resources. Doctors who treat well people are better remunerated.”

“Clinicians need to be vigilant to avoid colluding with those who have vested interests in some preventive activities.”

Lancet December 6, 2008; 372: 1997-99 “Viewpoint” essay, first author Jaun Gervas, Equipo CESCA, Madrid Spain.

I enjoyed this article. It reemphasizes the principle of individualization.

Preventive interventions are based on screening (testing for risk in asymptomatic individuals). Some “tests” are obvious (eg, increased risk is self-evident in smokers and obese sedentary patients). For these patients, lifestyle preventive interventions predominate. Patients find compliance difficult.

Patients should understand that prevention is based on a statistical analysis of a large number of subjects—the chance that the preventive intervention will indeed prevent the disease. (However, if the disease is prevented, the patient will never know it.) RTJ

An article in BMJ April 29, 2006; 332: 1027-30 "Should we Screen for Depression?" Editorial by Simon Gilbody, University of York, UK comments on screening:

"All screening programmes do harm. Some do good as well"

The criteria for screening:

The condition should be an important health problem

The epidemiology and clinical course of the disease should be adequately understood

The screening test should be safe, precise, and validated; a suitable cut-off point should be defined and agreed

The test should be acceptable to the population

An effective treatment should be identified with evidence that early preventive intervention leads to better outcome

Clinical management of the condition should be optimized before the screening program is offered

High quality randomized, controlled trials should provide evidence that the screening program effectively reduces morbidity

The screening program should be clinically, socially, and ethically acceptable

The benefit should outweigh the physical and psychological harm

The cost should be economically balanced in relation to expenditure on medical care (value for money)

Screening for prostate cancer with PSA was considered a step forward and was widely encouraged when it was introduced. It has lost favor. It does not meet some of the requirements listed above. RTJ

==========

"Similar In Nearly All Clinical Outcomes."

12-2 CLINICAL EQUIVALENCE OF GENERIC AND BRAND-NAME DRUGS USED IN CARDIOVASCULAR DISEASE *A Systematic Review and Meta-analysis*

Rising prescription drug costs is straining budgets of patients and insurers, and directly contributing to adverse heath outcomes by reducing adherence to important medications.

To control spending, many payers and providers have encouraged substitution of generic drugs for brand-name drugs.

Generics are chemically equivalent to their brand-name counterparts in terms of active ingredients. They may differ in specific manufacturing processes. The FDA requires generics to be “biologically equivalent”—defined as absence of a significant difference in the availability of the active ingredients at the site of drug action. Bioequivalence can be established on the basis of the maximum serum concentration of the drug, the time until maximum concentration is reached, or the area under the curve based on serum concentration as a function of time.

There has been concern that “bioequivalent” generic and brand-name drugs may not be equivalent in their effects on various cardiovascular disease clinical parameters including physiological measures (eg, heart rate and BP), laboratory measurements, and outcomes. Of particular concern are drugs with a narrow therapeutic index; in which the effective dose and toxic dose are separated by a small difference in plasma concentration. Anecdotes have appeared in the lay press raising doubts about efficacy and safety of certain generics. Are generics inferior to brand-names?

This study evaluated comparisons of generics and brand-name drugs on clinical parameters of cardiovascular disease.

Conclusion: Evidence did not support the notion that brand-named drugs used in cardiovascular disease were superior to generics.

STUDY

1. Systematically reviewed studies from 1984-2008 comparing generic and brand-name drugs using clinical efficacy and safety endpoints. Included 47 articles in the analysis.
2. All studies reported a comparative evaluation of one brand name drug with a generic version produced by a distinct manufacturer. The comparative evaluation had to include measurement of at least one clinical efficacy or safety endpoint, a laboratory study, patient morbidity and mortality, or health system utilization.
3. Also systematically reviewed the content of editorials published during this time, which addresses generic substitution.

RESULTS

1. Wide therapeutic index (**WTI**) drugs:

   Considered 7 different drug classes (mainly beta-blockers, diuretics, and calcium blockers).

   Clinical equivalence was noted in randomized, controlled trials (RCTs) of:

   7 of 7 beta-blockers

   10 of 11 diuretics

5 of 7 calcium blockers

3 of 3 antiplatelet agents

2 of 2 of statins

1 of 1 ACE inhibitors

1 of 1 alpha blockers.

2. Narrow therapeutic index (NTI) drugs: :

Clinical equivalence was noted in RCTs of:

1 of 1 class I antiarrhythmic agents

5 of 5 warfarin.

3. Aggregate effect size indicated no evidence of superiority of brand-names vs generics.

4. Among 43 editorials, 23 (53%) expressed a negative view of generic drug substitution; 12 (28%) encouraged substitution of a generic. Among NTI drugs, 12 expressed a negative view; 4 supported substitution.

DISCUSSION

1. "The studies in our sample concluded that generic drugs and brand name cardiovascular drugs are similar in nearly all clinical outcomes." "Our results suggest that it is reasonable of physicians and patients to rely on the FDA bioequivalence rating as a proxy for clinical equivalence among a number of important cardiovascular drugs."

2. Fewer RCTs of WTI drugs were considered: statins, ACE inhibitors, antiplatelet agents, and alpha-blockers. This limits ability to reach similar conclusions in these drug classes.

3. Among 5 warfarin studies, 2 revealed transient differences in INR after changes from brand names to generics. There was no difference in clinical outcomes. "Taken as a whole, these results suggest that switching form brand name to generic coumadin is safe, although it may be useful to monitor the INR of higher-risk patients more closely during the switch period "

4. Most clinical outcomes were evaluated by testing a superiority hypothesis rather than a non-inferiority hypothesis. Statistical insignificance in the context of a superiority study does not allow one to conclude that the agents are equivalent, only that there is insufficient evidence available to conclude that the agents are different.

5. Many studies included disproportionately young and healthy subjects. There was limited data about older patients with multiple morbidities who were taking numerous medications.

6. Most studies were short-term and did not collect the data necessary to compare long-term outcomes.

7. These findings also support the use of formulary designs aimed at stimulating appropriate generic drug use.
8. Use of generics may decrease costs without adversely affecting outcomes.

Conclusion

Evidence does not support the notion that generic drugs used in cardiovascular disease are inferior to brand-name drugs.

A substantial number of editorials, however, counseled against interchangeability with generic drugs.

JAMA December 3, 2008; 300: 2514-26 Original investigation, first author Aaron S Kesselheim, Harvard Medical School, Boston Mass.

==========

Ispaghula, antispasmodics and peppermint oil should be considered

12-3 TREATMENT OF IRRITABLE BOWEL SYNDROME IN PRIMARY CARE:

Irritable bowel syndrome (**IBS**) is common and difficult to treat. A wide range of treatments is used: dietary exclusion; fiber supplements; probiotics; antispasmodic drugs; antidiarrheal agents; laxatives; antidepressants;; hypnotherapy; and cognitive behavioral therapy.

A high placebo response has been observed. This highlights our ignorance about the cause of IBS.

A systematic review in this issue of BMJ[1] summarizes the effect of three different agents: fiber, antispasmodic drugs, and peppermint oil.

The meta-analysis included data from over 2500 patients with IBS.

The number needed to treat to benefit one patient:

Fiber	12	(12 trials)
Antispasmodics	5	(22 trials)
Peppermint oil	2.5	(4 trials)

(All were more effective than placebo.)

This looks like good news. However, as always, the devil is in the details.

Fiber: Overall, the trials of fiber reported benefit. But only ispaghula[2] significantly reduced symptoms. (NNT = 6). Wheat bran was not beneficial. The effect was no longer significant when only the highest quality studies were analyzed. Nevertheless, these findings add support to the NICE

guideline, which advises against the use of insoluble fiber (eg, bran) and recommends use of soluble fiber such as ispaghula.

Antispasmodics: The analysis of antispasmodic drugs included studies on a dozen different drugs. The best evidence was for hyoscine (NNT = 3.5). Hyoscine butylbromide[3] is an antimuscarinic agent extracted from the cork wood tree. It is not widely used in the UK. It is available by prescription.

Peppermint oil: Available without a prescription. It seems to be the most promising agent (NNT = 2.5). There was a total of fewer than 400 participants in the trials. The three highest quality trials showed similar treatment effect, with little heterogeneity between trials.

The meta-analysis lacked information on the subtype of IBS (constipation predominant, diarrhea predominant, or alternating), drug dosage, and patterns of administration. It provided no guidance on patient selection for a particular agent. This limits clinical applicability.

The results should reawaken interest in the pharmacotherapy of IBS, and stimulate further research.

There may be a place for " N of 1 trials" in individual patients.

None of these data invalidate the importance of making a "holistic" diagnosis in IBS—that takes into account physical, psychological, and social factors—and of planning an integrated approach to treatment.

BMJ December 13, 2008; 337: 1361-62 Editorial by Roger Jones, King's College, London, UK

1 "Effect of Fibre, Antispasmodics, And Peppermint Oil In The Treatment Of Irritable Bowel Syndrome: Systematic Review And Meta-Analysis" BMJ December 13, 2008; 337: 1388-92 first author Alexander C Ford, McMaster University, Hamilton, Ontario, Canada.

Only randomized, controlled trials were considered.

"This systematic review and meta-analysis shows that ispaghula, antispasmodics, (particularly hyoscine), and peppermint oil are all effective treatment for irritable bowel syndrome. Many are safe and available over the counter but, with the advent of newer more expensive drugs, are often overlooked."

2 Psyllium ispaghula is one variety of the plant of the genus Plantago. Psyllium is the husk or seed from various species of the plant. It is considered a bulk laxative. It is a soluble fiber.

3 Hyoscine is scopolamine. My pharmacy stocks it.

==========

"Risks Are Systematically Underestimated Among Persons With Lower SES"

12-4 SOCIOECONOMIC STATUS AND CORONARY HEART DISEASE PREDICTION

Disparity in life expectancy between groups of individuals with low social economic status (**SES**) and those with high SES has been increasing. Much of this disparity is attributable to higher mortality from coronary heart disease (**CHD**) among persons with lower SES.

Risks are systematically underestimated among persons with lower SES.

Disparities arise because of: early life environment; material disadvantage; social and behavioral risk factors; access to care; costs; and health literacy. Low SES is also associated with impaired exercise capacity, abnormal heart rate recovery, and chronic social stress.

Current risk-based intervention strategies ignore the independent contribution of SES to CHD. The risk of low SES is independent of age, sex, diabetes, physical activity, diet, cholesterol, and bodyweight.

A study from Scotland reported that the Framingham risk score (FRS) underpredicted risk of CHD among persons with low SES. Predicted by the FRS, individuals living in communities with the lowest income had a 3% higher estimated risk than those living in the wealthiest communities. Actually, the risk was 41% higher.

Including social risk in CHD risk prediction may mitigate the underestimation of risk in those at low SES.

On balance, education may be the optimal SES measure.

Although recognition of the role of social risk is increasing, physicians remain reluctant to use SES as a risk marker. They may be because of uncertainty about the exact causal pathway between SES and CHD. Physicians may prefer to focus on individual behavioral and physiological risks rather than social risk factors.

We need better data from the USA.

JAMA December 10, 2008; 300: 2666-68 "Commentary", first author Kevin Fiscella, University of Rochester, NY.

==========

Screen Patients with CHD for Depression

12-5 ROUTINE DEPRESSION SCREENING ADVISED FOR PATIENT WITH CORONARY HEART DISEASE

Up to 20% of patients with myocardial infarction (**MI**) meet the criteria for major depression. Depression is not a "normal" occurrence after a MI.

The American Heart Association advises clinicians to regularly screen patients with CHD for depression. The American Psychiatric Association agrees.

Comorbidity of depression and CHD leads to worse outcomes for both conditions.

Depression in CHD patients retards recovery, lowers and reduces adherence to medication and cardiac rehabilitation.

The advisory recommends the simple screening test for depression:

1) Over the past 2 weeks have you had little interest in doing things?

2) How often have you been feeling down, depressed and hopeless?

If there is a positive response to either or both, go on to the Patients Health Questionnaire (PHQ-9)[1], which can be conducted in 5 minutes.

Treatment includes cognitive-behavior therapy and physical activity. SSRIs such as sertraline (Generic; *Zoloft*, Pfizer) and citalopram (Generic; *Celexa*, Forest) seem safe soon after an MI.

There is evidence that patients who do not get better from their depression are at high risk of dying.

JAMA November 26, 2008; 300: 2356-57 "Medical News and Perspective", commentary by Mike Mitka, JAMA Staff.

1 Go to Google for a copy

This commentary is linked to a study in this issue of JAMA "Depressive Symptoms, Health Behaviors, and Risk of Cardiovascular Events in Patients with Coronary Heart Disease" JAMA November 26, 2008 2379-88, first author Mary A Whooley, University of California, San Francisco.

The study concludes that the association between depressive symptoms and adverse cardiovascular events was largely explained by behavioral factors, particularly physical inactivity.

==========

"The Body's Response Is Systemic"

12-6 ORAL HEALTH—DIABETES LINK

Poor oral health can have significant effects on the health of the rest of the body.

When bacteria from periodontal disease (**PD**) are released into the blood stream, production of pro-inflammatory cytokines increases. The body's response is systemic.

The link between PD and heart disease is one of the most common associations.

Conditions within the oral cavity appear to have a particularly close relationship with diabetes.

Poor oral health may have adverse effects on diabetes.

The National Health and Nutrition Examination Survey (**NHANES**) reported in 2008 that individuals with PD were twice as likely to develop diabetes as persons without PD. In Pima Indians, PD was a strong predictor of mortality from diabetic nephropathy.

PD is associated with insulin resistance and higher levels of HbA1c.

Periodontal disease can make it more difficult to control diabetes.

When diabetic patients receive good dental care, there are substantial savings related to medical care.

The relationship goes both ways. Diabetes can lead to adverse changes in oral health.

Patients with diabetes are more susceptible to PD.

PD is more severe in patients with diabetes.

NHANES data indicates that women who develop gestational diabetes are at greater risk for developing PD.

There are many other oral complications of diabetes. If the blood glucose gets high, glucose levels in saliva rise, increasing cavity formation and yeast infections. Lichen planus and salivary gland dysfunction are also more common.

"For the first time ever, the American Diabetes Association has recommended that physicians ask patients when they last saw a dentist. If they had not seen one in the past year, the physician should recommend an oral examination."

JAMA December 3, 2008; 300: 2471-73 "Medical News and Perspective', commentary by Tracy Hampton, JAMA staff.

==========

"Think Twice, Or Even 3 Times."

12-7 SCREENING FOR PROSTATE CANCER AMONG MEN 75 YEARS OF AGE AND OLDER

Prostate cancer (**PC**) screening with prostate specific antigen (**PSA**) remains one of the most controversial issues in medicine.

The US Preventive Services Task Force (USPSTF) recently revised its recommendation regarding screening, concluding that "the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men *younger* than age 75 years".

Furthermore, it now "recommends *against* screening for prostate cancer in men age 75 years and older".

The new recommendations imply that clinicians should discuss the potential benefits and known harms of screening with men between age 50 and 74, but not necessarily with older men.

Why change the recommendations for men over age 75? The task force believes that at least a moderate amount of evidence now makes it possible to conclude that the known harms of screening outweigh the possible benefits in this age group.

This does not mean that PC is an unimportant problem among men 75 or older. In fact, 71% of deaths due to PC—almost 20 000 annually in the US—occur after age 75. This does not mean that no men over age 75 could possibly benefit from screening. There are some relatively healthy men in their late 70s who harbor high grade PC that is likely to kill them. Early detection and attempted curative treatment might prevent these men from dying from PC. So why not continue to offer screening after age 74?

The effectiveness of attempting curative treatment among men of this age appears to be low or negligible. A large study from Scandinavia reported that there was a small benefit of radical prostatectomy vs watchful waiting in men with clinically localized PC. The rate of death due to PC was 5% lower in the surgical group over 12 years (NNT about 20). However, in subgroup analysis, this level of effectiveness appeared to be confined to men age 65 and younger. Fewer than 10% of men in this trial had their PC diagnosed by PSA screening. The long average lag time between a detectable increase in the PSA level—5 to 10 years—and the development of clinical cancer, as well as the possibility of overdiagnosis associated with PSA screening, suggests that an even smaller benefit may result from screening.

Given the slow growth of most PCs, and the resultant long lead times between screening and detectability of clinical disease, men may need to live much longer than 10 years to reap the benefits of PSA screening. Preventing death from PC does not bestow immortality. The great majority of men over age 75 die of other causes. Even if a few deaths could be prevented within this time frame, the effect on overall mortality would be small.[1]

The benefits of screening attenuate with age. The harms increase. PSA levels are strongly age-dependent. At any given PSA threshold, older men will have substantially higher risks of both requiring a biopsy and being diagnosed with PC. (21% of men in their 70s would be expected to have a PSA level above 4.0 ng/L.)

The risks of postoperative death and complications from radical prostatectomy are age related, escalating above age 75.

Given the unfavorable trade-off between the possible benefits and known risks of screening after age 74, the editorialist believes the USPSTF recommendations are sound. Clinical judgment must be used in its application.

Prevalence of PSA screening in older men in the US remains high. “Think twice, or even 3 times.”

NEJM December 11, 2008; 359: 2515-16 “Perspective”, editorial by Michael J Barry, Harvard Medical School, Boston, Mass

1 I doubt individual primary care patients would be impressed by this argument. A better way of expressing would be to tell the patient that, if he develops PC at a late age, he is much more likely to die with the disease than because of it. RTJ

==========

Resulted In A Moderately Lower Hba1c Level.

12-8 EFFECT OF A LOW-GLYCEMIC INDEX OR A HIGH-CEREAL FIBER DIET ON TYPE 2 DIABETES

Diet and lifestyle changes can prevent onset, and improve control, of type 2 diabetes (**DM-2**).

A low-glycemic index diet (**L-GID**) has been reported to improve the control of diabetes; increase HDL-cholesterol; lower serum triglycerides and C-reactive protein concentrations; and reduce incidence of diabetes and overall cardiovascular events.

Acarbose (*Precose*; Bayer) inhibits glucose absorption. It effectively creates a L-GID. In high risk patients it has been reported to reduce the rate of progression of diabetes, incidence of hypertension, and risk of cardiovascular disease.

The relevance and practicality of applying the L-GID. to treatment of diabetes has been questioned.

This trial assessed the effect of a L-GID in patients with DM-2 treated with oral agents.

Conclusion: In patients with DM-2, a L-GID resulted in a moderately lower HbA1c.

STUDY

1. Randomized trial entered 210 volunteer patients with DM-2 (mean age = 61). All were taking oral antidiabetes drugs (other than acarbose). The drugs were continued. Baseline HbA1c ranged between 6.5% and 8.0%. (Mean = 7.1%)
2. None had clinically significant cardiovascular, renal, or liver disease.
3. Randomized to: 1) L-GID, or 2) high-cereal fiber diet as a control. The diets were structured

(*table 3 page 2747*) The L-GID. contained a glycemic index of 62, and a glycemic load of 141. The high fiber diet, a glycemic index of 86 and a glycemic load of 201.

4. Outcome measures = change in HbA1c and cardiovascular risk factors.
5. Follow up for 6 months. (About 20% of participants dropped out.) Analysis by intention-to-treat.

RESULTS

1. Mean outcomes:

	Baseline		6 months	
	High fiber	L-GID.	High fiber	L-GID.
HbA1c (%)	7.07	7.14	6.89 (-0.18%)	6.64 (-0.50%)
Fasting glucose (mg/dL)	141	139	137 (- 4)	128 (-11)
Body weight (kg)	87.8	87.0	86.2 (-1.8)	84.5 (-2.5)
High density cholesterol	43.1	41.9	42.8 (- 0.3)	43.6 (+1.7)

2. Adverse effects: None serious. Six patients in the L-GID group had clear evidence of hypoglycemia or low blood glucose.

DISCUSSION

1. Lowering the glycemic index improved glycemic control and increased HDL-cholesterol.
2. The change in HbA1c was modest, The investigators, however, believe this has clinical relevance.
3. The intervention also was associated with weight loss. (Weight *gain* often accompanies treatment with glucose-lowering medications.)
4. These improvements were achieved in individuals already treated with oral drugs.
5. The high-cereal fiber diet may have been more than a control. Increasing fiber intake has been associated with reduced incidence of diabetes and CHD.

CONCLUSION

Treatment of DM-2 for 6 months with a L-GID resulted in a moderately lower HbA1c level.

L-GID may be useful as part of the strategy to improve glycemic control in patients with DM-2 who are taking antidiabetes drugs.

JAMA December 17, 2008; 2742-53 Original investigation, first author David J A Jenkins, University of Toronto, Canada

==========