PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

FEBRUARY 2006

SOMATIZATION: ***Do Primary Care Clinicians Facilitate it?***

PLACEBO EFFECT: Sham Device Versus Inert Pill.

INHALED INSULIN APPROVED IN EUROPE AND UNITED STATES

CALCIUM PLUS VITAMIN D AND RISK OF FRACTURES IN OLDER WOMEN

CONJUGATED EQUINE ESTROGENS AND CORONARY HEART DISEASE: No Harm; no Benefit

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IS MELATONIN INEFFECTIVE?

IS MELATONIN LEGAL FICTION? DOES IT HELP PEOPLE SLEEP?

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FONDAPARINUX: a Promising New Anticoagulant

EARLY CLINICAL RECOGNITION OF MENINGOCOCCAL DISEASE—Life Saving

COCOA INTAKE, BLOOD PRESSURE, AND CARDIOVASCULAR MORTALITY

JAMA, NEJM, BMJ, LANCET

ARCHIVES INTERNAL MEDICINE

ANNALS INTERNAL MEDICINE

www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.

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This document is divided into two parts

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

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 5 years can be accessed at www.practicalpointers.org

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

HIGHLIGHTS AND *EDITORIAL COMMENTS* FEBRUARY 2006

Begin Consideration of Both Biomedical and Psychosocial Causes at the Onset of A New Consultation

2-1 SOMATIZATION: ***A Joint Responsibility of Doctor and Patient***

Most studies of somatization focus on patients' characteristics. There is a widespread belief that inappropriate symptomatic treatment has to be attributed to patients' beliefs that symptoms are caused by physical disease, their insistence on biomedical intervention, and their denial of psychosocial needs. The possibility that doctors play a part has been largely ignored.

A detailed analysis of general practice patients with unexplained symptoms found that physical interventions were proposed more often by doctors than by patients. Almost all patients provided clues to their psychological needs. Most doctors suggested that one or more physical diseases might be present. The authors conclude that the explanation for the high level of physical intervention in these patients lies in doctors' responses rather than patients' demands.

Some studies show that most doctors adapt their biomedical interventions at least partly to presumed patient preferences. They may overestimate their patients' wishes in this regard, particularly regarding prescriptions and referrals.

The mantra "First of all, do no harm" seems to be replaced by "First of all, don't miss a medical diagnosis".

The editorialists conclude that a solution may lie in a comprehensive approach right from the start in which a biomedical track and a psychosocial track are jointly explored. This may give the patient confidence that all biomedical needs are rightly addressed while at the same time the floor is open for discussing psychological issues.

Primary care clinicians—Do you agree that we are partly responsible for the overuse of tests and consultation—not only for patients with suspected somatization,, but for patients in general ?

These patients are indeed suffering. How best can primary care clinicians help them? I believe mainly by listening to the patient. The art of medicine is indeed long and difficult.

Device Outperforms Pill

2-2 SHAM DEVICE VERSUS INERT PILL: ***Randomized Trial Of Two Placebo Treatments.***

This trial, in patients with arm pain, investigated whether a sham acupuncture needle had a greater placebo effect than an inert pill.

Participants (n = 119) were community dwellers who had arm pain due to repetitive use that had lasted at least 3 months despite treatment. All had pain scores of 3 or more on a 10-point pain scale.

Randomized to 1) acupuncture with a sham device twice a week for 6 weeks, and 2) an inert placebo pill once daily for 8 weeks.

Pain scores and the symptom severity scale decreased significantly more in the sham group than in the pill group.(-0.33 vs -0.15; and -0.007 vs -0.05) (In the sham acupuncture group, the downward slope in the 10-point pain scale each week was significantly steeper than the downward slope in the placebo pill group.)

Differences in grip strength and arm function were not significant.

Nocebo effects were totally different in the two groups, and clearly mimicked the information given at informed consent. Sham acupuncture subjects were told that their pain might be temporarily aggravated: placebo pill subjects were told that they might experience sleepiness, dry mouth, dizziness, and restlessness. One quarter to one third of subjects reported such adverse effects. “Our findings contribute to the debate on the influence of information provided at informed consent and subsequent reported adverse effects.” “We found that reported side effects perfectly mirrored the information provided to participants.”

“Placebo effects seem to be malleable, and depend on the behaviors embedded in medical rituals.”

The same group commented in 1998 “No longer is it sufficient for a therapy to work; it must be better than placebo.”

Placebos are both fascinating and powerful. Indeed, I believe at times the placebo effect is the primary care clinician’s best friend. I would not discourage placebo use in a patient who perceives benefit—provided the placebo is not harmful and does not preclude other therapy of proven benefit.

Although we may argue about whether it is ethical to prescribe a placebo, I believe many, if not most, primary care clinicians will occasionally prescribe a drug for which they have little or no expectation of pharmacologic benefit.

To assess the power of the placebo effect, it is necessary to compare a group of patients who receive no-treatment and no-placebo, with a group receiving a placebo.

A part of the effect of all active drugs is due to the placebo effect.

The strength of the placebo depends on its form (as in this study), the enthusiasm and belief of the clinician, and the culture and belief of the patient. If 1000 patients are given a placebo, and 1) 500 enthusiastically and conscientiously take it, and 2) 500 patients take it irregularly, without complying with the regular schedule, outcomes in group 1) will be better than in group 2).

There is no doubt that totally (pharmacologically) inactive substances can produce demonstrable effects on brain function. Inert pills and devices can have harmful (nocebo) effects.

"First New Insulin Delivery System since The Discovery Of Insulin In The 1920s". But use with reservations.

2-3 INHALED INSULIN APPROVED IN EUROPE AND UNITED STATES

An inhaled form of human insulin (*Exubera*) has been approved for treatment of both type 1 and type 2 diabetes.

This brief comment lists some cautions. It is contraindicated in smokers. It is not recommended for patients with asthma, bronchitis and emphysema. It has been associated with increases in cough, dyspnea, sinusitis, and pharyngitis. And is also associated with a small mean decrease in FEV1.

There are concerns about erratic absorption. It may fail to control postprandial glucose as well as subcutaneous insulin.

It may be especially indicated for patients "who absolutely refuse to take shots".

I believe primary care clinicians should wait for a year or two of observation of use in the general population before prescribing it.

Is this the final word on calcium + vitamin D supplementation to reduce risk of fracture ?

2-4 CALCIUM PLUS VITAMIN D SUPPLEMENTATION AND RISK OF FRACTURES IN OLDER WOMEN

This trial tested the hypothesis that calcium + vitamin D **(C + D)** supplementation, begun at an advanced age in women, would lower risk of hip fractures and other fractures as compared with placebo.

The Women's Health Initiative recruited over 36 000 postmenopausal women age 50 to 79 (mean age = 62 at baseline). All were living in the community and were considered healthy.

Randomized to: 1) 1000 mg calcium + 400 IU vitamin D daily, or 2) placebo.

Bone mineral density was greater in the calcium + vitamin D group at year 7 by 1%.

Fracture rate overall*	Ca + D	Placebo
Hip	175	199
Vertebral	181	197
Forearm of wrist	565	557
Total	2102	2158

(*Intention-to-treat. No statistical difference between groups.)

Among women who were adherent (ie, took at least 80% of their study medication), C + D supplementation resulted in a 29% reduction in hip fracture—68 in the C + D group vs 99 in the placebo group (95% confidence interval = 0.52-0.97—statistically significant).

"The trial demonstrated that calcium with vitamin D supplementation diminishes bone loss at the hip, but the observed 12 percent reduction in the incidence of hip fracture (the primary outcome) was not statistically significant." "It is plausible that there was a benefit only among women who adhere to the study treatment." Only 59% of women were still taking the intended dose of the study medication at the end of the trial.

Although the statistically null primary effect argues against recommending universal calcium with vitamin D supplementation, the findings provided evidence of a positive effect of calcium with vitamin D on bone health in older postmenopausal women

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I would amend the conclusion to state that calcium and vitamin D supplementation did not significantly reduce hip fracture when begun at age 62. I would not expect much reduction in fractures in women when C + D supplementation is begun long after the menopause. Intakes of C and D are almost universally deficient in the USA at all ages. Efforts to develop and maintain healthy bone structure are a life-time endeavor. Primary care clinicians should ensure their patients achieve adequate intakes beginning in childhood.

The benefit/harm-cost of C + D supplementation is, I believe, very high. Entering menopause with healthy bones will reduce hip fractures and alleviate the frequency of disabling kyphosis which plagues many older women.

No Benefit; No Harm

2-5 CONJUGATED EQUINE ESTROGENS AND CORONARY HEART DISEASE *The Women's Health Study*

Recent randomized trials of hormone replacement therapy (**HRT)** with conjugated equine estrogens (CEE) + medroxyprogesterone reported no protection against coronary heart disease **(CHD),** and may have increased risk.

This associated, but separate, trial considered women who had experienced a hysterectomy and were eligible to receive unopposed CEE . This is the final report of the trial.

Randomized over 10 000 women (mean age = 64) to; 1) unopposed CEE 0.625 mg daily, or
2) placebo.

At 7 years, 201 coronary events occurred in the CEE group, vs 217 in the placebo group. (No clinical or statistical difference.)

This study is important. It applies to the many women who have undergone hysterectomy whose menopausal symptoms are disturbing. It was reported without editorial comment as the last article in this issue of Archives. I believe it deserved wider distribution. Estrogens-alone did not lead to excess CVD risk.

Observational studies long reported that HRT protected against cardiovascular disease. This, it finally turned out, was due to the bias of the "healthy user".

The original reports of WHI studies [1,2] *(CEE + progestin) were widely distributed and caused much comment. They refuted the long-held view that HRT would protect against cardiovascular disease. The main conclusion was that HRT should not be used to prevent CVD.*

Many doctors then discontinued prescribing CEE + progestin. And many women stopped taking it (despite continuing menopausal symptoms), and despite the low excess risk of cardiovascular events over 5 years.

Associated With Significant Deficits in Cognitive Functioning

2-6 NON-DEGENERATIVE MILD COGNITIVE IMPAIRMENT IN ELDERLY PEOPLE AND USE OF ANTICHOLINERGIC DRUGS

Dysfunction of the cholinergic system has a detrimental effect on cognitive performance. The anticholinergic agent, scopolamine, reduces hyppocampal activation, and, when given to young adults, produces cognitive defects characteristic of aging-related changes, rather than dementia.

Drug consumption in elderly people is high. Many commonly prescribed drugs have anticholinergic effects (antiemetics, antispasmodics, bronchodilators, antiarrhythmic drugs, antihistamines, analgesics, antihypertensives, antiparkinsonian agents, corticosteroids, skeletal muscle relaxants, ulcer drugs, and psychotropic drugs). These are likely to have a more toxic effect in an aging brain because of increased permeability of the blood-brain barrier, slower metabolism and drug elimination, and polypharmacy.

Doctors commonly fail to associate cognitive dysfunction in elderly people with anticholinergic agents. They also underestimate anticholinergic toxicity, and prescribe such drugs at high doses. An increasing number of such compounds are available without prescription.

This study tested whether drug-induced anticholinergic burden is associated with cognitive dysfunction.

Of the 372 subjects, 51 (14%) were taking at least one anticholinergic drug at baseline. None were taking acetylcholinesterase inhibitors. At the end of the year, 30 of 51 were still taking the drugs regularly.

Compared with the 297 non-users, the 30 continuing users had poorer performance on reaction time, attention, memory, visuospatial construction, and language tasks. 80% were classified as having mild cognitive impairment, compared with 35% of non-users.

This is an important contribution. I was not aware that so many drugs have anticholinergic activity. I believe also that few primary care clinicians are aware of them.

Before assuming that your patient has early dementia from Alzheimer's disease and prescribing a acetylcholinesterase inhibitor, consider if any drug you are prescribing could be related to beginning "dementia".

The message applies to many other drugs used in geriatric practice. Many carry unsuspected and undetected adverse effects in some individuals. Primary care clinicians should be constantly aware that adverse drug effects may occur more frequently in the elderly, and may present in diverse ways. Continually ask—could any drug I prescribed adversely affect this patient? Or is any non-prescription drug?

I hope a follow-up study will measure effects of discontinuing these drugs.

Is Melatonin Ineffective?

2-7 EFFICACY AND SAFETY OF EXOGENOUS MELATONIN FOR SECONDARY SLEEP DISORDERS AND SLEEP DISORDERS ACCOMPANYING SLEEP RESTRICTION

Melatonin is classified as a "dietary supplement"[1]. It is available without a prescription.

This systematic review assessed efficacy and safety of melatonin for managing secondary sleep disorders and sleep restriction.

A. Secondary sleep disorders:

Sleep onset latency (amount of time between lying down to sleep and onset of sleep): Six trials (97 participants) showed no evidence that melatonin had an effect on sleep onset latency. The combined estimate favored melatonin by a mean of 13 minutes. However, the confidence interval = -27 to 0.9 minutes, and thus did not quite reach the 0.05 significance level. Heterogeneity between studies was substantial. When one outlier which favored placebo was eliminated, the result became statistically significant (CI = -26 min to – 8 min)

Other efficacy outcomes: Six trials showed a significant effect favoring melatonin. (Weighted mean difference = 1.9%; confidence interval = 0.5 to 3.3) "However, the effect seems not to be clinically important."[2]

B. Sleep restriction:

Sleep onset latency: Nine trial produced a combined estimate that favored melatonin, but was not statistically significant. Mean difference = -1 minute; confidence interval = -2.7 min to 0.3 min.

Other efficacy outcomes: For sleep efficiency (time spent in bed asleep), the combined estimate from 5 trials showed no statistically significant difference between melatonin and placebo. Weighted mean difference = 0.5%; confidence interval = -0.6% to 1.6%

Safety over 3 months or less:

The most commonly reported adverse effects were headache, dizziness, nausea, and drowsiness. The occurrence of these outcomes did not differ between groups.

Conclusion of the meta-analysis: "There is no evidence that melatonin is effective in treating secondary sleep disorders, or sleep disorders accompanying sleep restriction such as jet lag or shift work disorder."

This is a sophisticated statistical study. I congratulate the investigators on their diligence. Is it the last word on melatonin? I think not.

1 *"Dietary supplements" are not standardized, are not pure, and may by adulterated. Although melatonin is classified as a "dietary supplement", it is an exception. It is a simple, defined chemical entity which may permit standardization of purity and dose. The dose may have to be established on a person-to-person basis. The various studies cited did not use a standardized form and dose of melatonin.*

2 *Clinical effectiveness must be judged on the basis of response by an individual patient, not on p values, not on confidence intervals. Patients know nothing about p values. There will always be outliers from the mean response. For some subjects, melatonin was associated with shortening the time to go to sleep and lengthening the time spent asleep. Undoubtedly, there is a large placebo effect of melatonin. But, in view of its safety, if my patient judged his sleep to be improved by the melatonin, I would not dispute his observation or/NOR discourage him from taking it. If a patient who had never taken melatonin expressed a desire to try it, I would not discourage her. I would suggest she purchase it in a national drug store chain, not by mail or over the Internet. My pharmacy sells 3 mg melatonin at $13 for 240 tablets.*

A new drug for insomnia has been released by the FDA—ramelteon (Rozerem). It is a melatonin agonist, targeting two melatonin receptors in the brain. 1) MT1 receptor is thought to regulate sleepiness, and 2) MT2 receptor is thought to help the body shift between phases of day and night. It has been reported to modestly decrease the time it takes to reach persistent sleep and to modestly increase the total sleep time. It is available as 8 mg tablets.

Purity and dosage is regulated by the FDA. It is classified as a non-scheduled drug. The information provided by the company (Takeda, Japan) claims there is no risk of abuse or dependence. Withdrawal effects have not been reported.

Compared with melatonin: 1) ramelteon may have the advantage of being certified as pure and with an established dose, 2) ramelteon has the disadvantage of a shorter time of use by the general population. Some adverse effects may yet appear.

(Information gleaned from the internet via GOOGLE.)

Is Melatonin Legal Fiction?

2-8 DOES MELATONIN HELP PEOPLE SLEEP?

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

"In North America, melatonin is a popular wonder drug which has legal status and a 'nutritional' supplement, although that is legal fiction." As a result, it is not regulated as a medicine, and is advertised and sold widely—in pharmacies, health food shops, and on the internet. Millions of people use it mostly because they believe it will help them sleep.

The Dietary Supplement Health and Education Act, passed by the US Congress (1994), prevents the FDA from monitoring the quality and safety of "dietary supplements" before marketing. Supplements do not have to be dietary components.

The great majority of nostrums advertised and promoted to the general public by charlatans are taken by millions and are indeed legal fiction. They are not "nutritional" and they are not "supplements". They are not standardized. They are not pure. Many are purposely adulterated. Melatonin may be an exception. It is a simple, defined chemical entity which may permit standardization of purity and dose. The dose may have to be established on a person-to-person basis. The various studies cited in the article did not use a standardized form and dose of melatonin. Used properly, as for jet lag, melatonin should be taken at the time night begins at the place of destination.

Combined G and C May Be Effective In the Subgroup with Moderate-To-Severe Pain.

2-9 GLUCOSAMINE, CHONDROITIN SULFATE, AND THE TWO IN COMBINATION FOR PAINFUL KNEE ARTHRITIS

This randomized, double-blind, placebo-controlled trial compared glucosamine sulfate (G), chondroitin (C), both, celecoxib, and placebo for 6 months in over 1500 patients with knee osteoarthritis.

Product selection: The study was conducted under an investigational new drug application. As such, C and G were subject to pharmaceutical regulation by the FDA. Ingredients were tested for purity, potency and quality. **1**

Primary outcome = a 20% decrease in pain from baseline to 24 weeks based on a pain score.

Overall, for all randomized patients, C and G were *not* significantly better than placebo in reducing knee pain by 20%. Change in WOMAC pain score for placebo = -86 points; for G + C = -100 points.

The rate of response to placebo was high (60% reported a decrease in pain of 20% or more). As compared with placebo, the rate of response to G was 4% higher. And the rate of response to C was 5% higher. The rate of response to both C and G combined was 10% higher. (Not statistically significant.)

Overall, response to celecoxib was 10% higher than to placebo. And response time was much faster than for C and G.

For patients with moderate-to-severe pain, the rate of response to C + G combined was significantly higher than for placebo (79% vs 54%). Change in *mean* WOMAC pain scores from baseline to end of follow=-up = -123 points in the placebo group vs -153 points in the C + G group. (Statistically significant.)

For patients with moderate-to-severe pain, G +C was associated with a *greater* reduction in pain than celecoxib: - 177 points vs - 153 points.

A 20% reduction in pain seems a very modest goal.

1 *This is unusual. Most studies of "dietary supplements" do not screen products so carefully. This study was detailed, carefully crafted, executed, and analyzed from a statistical standpoint.*

2 *Does lack of "statistical" significance preclude a prescription? I believe not. There will always be patients whose response to treatment deviates from the mean, either less favorably or more favorably. Response to C + G must be evaluated in an individual patient.*

Would I prescribe C + G for a patient with OA pain? I would prescribe acetaminophen first. In view of the safety of C +G, I would mention the combination as a possibility for the patient to consider—at least to try.

I would suggest they purchase the preparation at a national-chain pharmacy rather than by mail or on the internet. I believe it would be more likely to be as labeled.

Although primary care clinicians may not admit it, I believe many do indeed rely on the placebo effect, at least accept it when a patient reports improvement.

At my pharmacy, G (1500 mg)+ c (1200 mg) costs $32 for 120 tablets. At times, it is on sale at about half price. Celebrex 200 mg costs $ 3.19 each

A Promising Anticoagulant. Long-Term Efficacy Not Established.

2-10 EFFICACY AND SAFETY OF FONDAPARINUX FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN OLDER ACUTE MEDICAL PATIENTS

"Most patients who die from pulmonary embolism **(PE)** as a complication of being admitted to hospital are medical patients." Around 10% of deaths are due to PE.

Fondaparinux (*Arixtra*; Glaxco SmithKline) is a synthetic, selective inhibitor of factor Xa. It effectively reduces postoperative venous thromboembolism **(VTE)** after orthopedic surgery.

This study determined the short-term efficacy and safety of fondaparinux in older, acutely ill *medical* inpatients. Randomized within 48 hours to: 1) fondaparinux, or 2) placebo.. Doses were given subcutaneously daily (2.5 mg fondaparinux or 0.5 mg saline).

A. Primary efficacy outcome *for first 15 days only*:

	Fondaparinux	Placebo
Any VTE	18	29
Proximal deep vein thrombosis	5	7
Distal deep vein thrombosis	13	22
Fatal PE	0	5
Total	18/321 (5.6%)	34/323 (10.5%)

(NNT to prevent one VTE = 20.)

B. Symptomatic VTE *up to day 32*:

	Fondaparinux	Placebo
Symptomatic deep vein thrombosis	0	0
Non-fatal pulmonary embolism	1	4
Fatal pulmonary embolism	3	7

Ten *additional* cases of PE occurred during follow-up after day 15—4 in the fondaparinux group, 6 in the placebo group. (Three in the fondaparinux group were fatal.).

Major bleeding occurred in one patient in each group. (0.2%) [1]

Two thirds of the clinically apparent events and half of the fatal PE were observed *after* the initial 6 to 14 day study period. This supports the need to evaluate extended prophylaxis in medical patients.[2]

I abstracted this article mainly to introduce what may become a major breakthrough. Two new oral Xa inhibitors are in the works.

1 *If the risk of major bleeding is indeed lower with fondaparinux, it would be a major benefit. Watch for further studies.*

2 *Note that the study focused on outcomes over 2 weeks only. The risk of VTE in these very ill older patients extends far beyond. The investigators note that VTE occurred frequently after the study period. Some were fatal. The question remains: How long must fondaparinux be continued in these medical patients? And for how long? . Duration of therapy for only 2 weeks adds relatively little overall protection.*

Look For Early Signs Of Sepsis: Leg Pains, Cold Hands and Feet (Despite Fever) , Abnormal Skin Color

2-11 CLINICAL RECOGNITION OF MENINGOCOCCAL DISEASE IN CHILDREN AND ADOLESCENTS

Meningococcal disease **(MD)** is a rapidly progressive infection of global importance. MD is initially misdiagnosed. The infection can progress from initial symptoms to death within hours. Diagnosis must be made as early as possible. The diagnosis often depends on textbook descriptions of classic features such as hemorrhagic rash, meningism, and impaired consciousness. These signs appear late in the course of the disease.

This study determined the frequency and time of onset of clinical features of MD. Questionnaire obtained data from parents and primary care records for the course of illness before hospital admission in 448 children age 16 and younger with MD. (103 were fatal.)

Calculated the number of hours from the onset of illness to the initial consultation, and to hospital admission (or to death before admission).

Most children had only non-specific symptoms in the first 4 to 6 hours, but were close to death by 24 hours.

Three quarters of children had early symptoms of sepsis.

In all age groups, the first *specific* clinical features were signs of sepsis—leg pain, cold hands and feet, and/or abnormal skin color (pallor or mottling). Most of these symptoms appeared at a median time of 8 hours—before the first medical contact. This was much earlier than the median time to hospital admission (19 hours).

Classical symptoms of rash, meningism, and impaired consciousness appeared late. (median onset = 13 to 22 hours).

"We believe our evidence is sufficiently robust to argue that we need a diagnostic paradigm shift."

The article reported that 50% of children were referred to the hospital at the first consultation. These clinicians were sharp!

Primary care physicians in the UK have been encouraged to carry penicillin in their bags, and to administer it immediately and empirically to children who appear very ill as efforts to admit to the hospital are begun. The benefit/harm-cost ratio of this approach may be high. It may be life-saving.

I would add another non-specific early sign—does the child appear very ill?

In a career, an individual primary care clinician may never encounter a patient with MD early enough to suspect and act on the possibility of MD. If the occasion arises, recognition may be life-saving.

Does a High Intake of Chocolate Reduce Risk of Death?

2-12 COCOA INTAKE, BLOOD PRESSURE, AND CARDIOVASCULAR MORTALITY

This study estimated intake of cocoa from the habitual consumption of cocoa-containing foods, and evaluated whether intake was inversely related to BP and CVD and all-cause mortality in a cohort of elderly men.

Used data of 470 elderly men (mean age at baseline = 72). All were free of chronic diseases at baseline (1985).

Assessed habitual food consumption by dietary history at 5-year intervals. This included consumption of cocoa-containing foods. Chocolate confectionary contributed about 2/3 of the total cocoa intake.

Ascertained causes of death during 15 years of follow-up.

Mean blood pressure highest tertile of cocoa use vs lowest tertile of use:

A. Mean systolic was 3.7 mmHg lower.

B. Mean diastolic was 2.1 mmHg lower.

	Tertiles of cocoa intake		
	Lowest (0.5 g/d)	Middle (0.5-2.25 g/d)	Highest (> 2.3 g/d)
No of subjects	165	149	156
Cocoa median g/d	0	0.92	4.2

Relative risk (RR) of death:

A Cardiovascular death (CVD): highest tertile compared with lowest tertile of cocoa use = 0.50.

B. All-cause mortality: highest tertile vs lowest tertile of cocoa use = 0.53.

(These RRs resulted from a model which adjusted for 19 possible confounders. RTJ)*

"In the present study, usual daily cocoa intake was inversely related to blood pressure."

"In prospective analysis, usual cocoa intake was associated with a 45% to 50% lower risk of cardiovascular and all-cause death."

The results are provocative, but unrealistic. I doubt the investigators really believe that cocoa is related to a 50% reduction in mortality. The observational study assumed many adjustments for possible confounding variables. It followed a relatively small number of subjects.

I can visualize a report in the lay press—"Chocolate reduces risk of death by 50%". Conflicting reports of medical studies result in an increasingly skeptical public.

ABSTRACTS FEBRUARY 2006

Begin Consideration of Both Biomedical and Psychosocial Causes at the Onset of A New Consultation

2-1 SOMATIZATION: ***A Joint Responsibility of Doctor and Patient***

Patients with unexplained symptoms are common. They are often portrayed as “difficult” and “heartsink”, a burden to the doctor as well as to the health care system. They show resistance to psychological explanations of their suffering and are always in quest of biomedical cause. This results in excessive use of heath-care services and risks of iatrogenic harm.

Most studies of somatization focus on patients’ characteristics. There is a widespread belief that inappropriate symptomatic treatment has to be attributed to patients’ beliefs that symptoms are caused by physical disease, their insistence on biomedical intervention, and their denial of psychosocial needs. The possibility that doctors play a part has been largely ignored.

A recent study claims that the doctor is often responsible for the disproportionate levels of somatic interventions in these patients. A detailed analysis of general practice patients with unexplained symptoms found that physical interventions were proposed more often by doctors than by patients. Almost all patients provided clues to their psychological needs. Most doctors suggested that on or more physical disease might be present. The authors conclude that the explanation for the high level of physical intervention in these patients lies in doctors’ responses rather than patients’ demands.

Further analysis of the interviews did reveal that, although doctors did indeed propose biomedical interventions, about two thirds also proposed non-medical explanations. And about 70% of patients proposed some biomedical intervention. Both were active in advocating biomedical interventions.

Some studies show that most doctors adapt their biomedical interventions at least partly to presumed patient preferences. They may overestimate their patients’ wishes in this regard, particularly regarding prescriptions and referrals.

The truth is that both patient and doctor have a preoccupation with finding biomedical causes; patients because of fear of serious diseases, and doctors because of professional pride and fear of missing a medical diagnosis with potential judicial consequences. The mantra “First of all, do no harm” seems to be replaced by “First of all, don’t miss a medical diagnosis”.

“There is a certain tension between these two guiding principles.”

The editorialists conclude that a solution may lie in a comprehensive approach right from the start in which a biomedical track and a psychosocial track are jointly explored. This may give the patient confidence that all biomedical needs are rightly addressed while at the same time the floor is open for discussing psychological issues. Most patients are willing to discuss psychological issues at the beginning of a new illness episode, but not after all medical examinations have failed. At that point, a psychological explanation is experienced as a second-rate explanation by which many patients feel offended and humiliated.

Lancet February 11, 2006; 367: 452-54 “Comment”, editorial, first author J M Bensing, Netherlands Institute for Health Services Research, Utrecht.

2-2 SHAM DEVICE VERSUS INERT PILL: *Randomized Trial Of Two Placebo Treatments*.

A National Institutes of Health conference declared that understanding how placebo effects are modulated is an urgent priority. Devices are thought to have enhanced placebo effects.

This trial, in patients with arm pain, investigated whether a sham device (a validated sham acupuncture needle) had a greater placebo effect than an inert pill.

Conclusion: The sham device had greater effects than the placebo pill.

STUDY

1. A single-blind, randomized-controlled trial compared sham acupuncture device vs placebo pill.
2. Participants (n = 119) were community dwellers who had arm pain (due to repetitive use) that had lasted at least 3 months despite treatment. All had pain scores of 3 or more on a 10-point pain scale.
3. Randomized to 1) acupuncture with a validated sham device twice a week for 6 weeks, and 2) an inert placebo pill once daily for 8 weeks.
4. The sham device looks exactly like a real acupuncture needle. When the needle is "inserted into the skin" participants think they see needle penetration and feel needle penetration pain. But the needle has a blunt tip, and retracts into a hollow shaft handle.
5. Main outcome measure = arm pain measured on a 10-point scale. Secondary outcomes = symptoms on a symptom severity scale, function measured on a function scale, and grip strength.

RESULTS

1. Pain scores and the symptom severity scale decreased significantly more in the sham group than in the pill group (-0.33 vs -0.15; and -0.007 vs -0.05). (In the sham acupuncture group, the downward slope in the 10-point pain scale each week was significantly steeper than the downward slope in the placebo pill group.)
2. Differences in grip strength and arm function were not significant.
3. Nocebo effects were totally different in the two groups and clearly mimicked the information given at informed consent. Sham acupuncture subjects were told that their pain might be temporarily aggravated: placebo pill subjects were told that they might experience sleepiness, dry mouth, dizziness, and restlessness. One quarter to one third of subjects reported such adverse effects.

DISCUSSION

1. Recent mechanism studies of placebo treatments have shown that placebo effects go beyond spontaneous fluctuations in symptoms (ie, beyond the natural evolution of disease, spontaneous remission, and regression to the mean).
2. Many studies have been accompanied by deceptive expectations—ie, subjects being told that the placebo was a "potent pain medication".
3. "If spontaneous remission alone accounted for our findings, the type of placebo should have made no difference, and we should not have been able to detect a difference between the device and pill."
4. That the differential placebo effect was confined to self-reported measures (and not grip strength) suggests

the effect that may be confined to subjective outcomes.

5. "Our findings contribute to the debate on the influence of information provided at informed consent and subsequent reported adverse effects." "We found that reported side effects perfectly mirrored the information provided to participants."
6. "Placebo effects seem to be malleable, and depend on the behaviors embedded in medical rituals."

CONCLUSION

A sham acupuncture device had greater effects than a placebo pill on self-reported pain and severity of symptoms over the entire course of treatment.

BMJ February 18, 2006; 332: 391-94 Original investigation ,first author Ted J Kaptchuk, Harvard Medical School, Boston Mass.

The study was somewhat more complex than I have indicated. It contained a run-in period of 2 weeks comparing the sham acupuncture vs placebo pill vs a third arm—amitriptyline. I abstracted the period of 6 weeks after amitriptyline was discontinued and the sham acupuncture was compared with placebo pill. I believe this does not in any way invalidate the results reported. RTJ

"First New Insulin Delivery System since The Discovery Of Insulin In The 1920s". But use with reservations.

2-3 INHALED INSULIN APPROVED IN EUROPE AND UNITED STATES

An inhaled form of human insulin (*Exubera*) has been approved for treatment of both type 1 and type 2 diabetes. The FDA hailed it as the "first new insulin delivery system since the discovery of insulin in the 1920s".

The FDA has specified that it is contraindicated in smokers and in patients who have smoked in the preceding 6 months. It is not recommended for patients with asthma, bronchitis, and emphysema. There are concerns about pulmonary effects and erratic absorption, even in patients exposed to secondhand smoke.

Tests have reported that it lowered the HbA1c comparably with subcutaneous insulin. (23% and 22%).

Critics say that *Exubera* offers no advantage over injected insulin. It fails to control postprandial glucose as well as injected insulin. FDA briefing documents show that two-hour postprandial glucose levels increased by 1.3 mmol/L (+23 mg/dL) in the inhaled group and decreased by 0.5 mmol/L
(- 9 mg/dL) in the injection group. Postprandial glucose control is a target for intensive diabetes control because it is associated with risk of cardiovascular disease. Erratic absorption and complex dosing conversions could lead to problems.

Inhaled insulin has been associated with increases in cough, dyspnea, sinusitis, and pharyngitis. It is also associated with a small mean decrease in FEV1. *Exubera's* label instructs patients to have pulmonary function tests before starting.

It is not known if these adverse effects are reversible after discontinuing.

The new drug may be especially indicated for patients "who absolutely refuse to take shots".

BMJ "News" report by Jeanne Lenzer, New York correspondent.

2-4 CALCIUM PLUS VITAMIN D SUPPLEMENTATION AND RISK OF FRACTURES IN OLDER WOMEN

In postmenopausal women, evidence from observational studies and meta-analyses of calcium and vitamin D with respect to hip and other fractures is limited.

When this trial was designed (in the early 1990s) guidelines recommended daily intakes of 800 to 1200 mg of calcium and 400 IU of vitamin D for prevention of osteoporosis. Many American women consume less.

This trial tested the hypothesis that calcium + vitamin D (C + D) supplementation in women, begun at an advanced age, would lower risk of hip and other fractures as compared with placebo.

Conclusion: C + D resulted in a small improvement in hip bone denisity, but it did not reduce hip fracture.

STUDY

1. The Women's Health Initiative recruited over 36 000 postmenopausal women age 50 to 79 (mean age = 62 at baseline; 37% age 50 to 59; 45% age 60-69; 18% 70 to 79). All were living in the community and were considered healthy.
2. Randomized to: 1) 1000 mg calcium + 400 IU vitamin D daily, or 2) placebo.
3. Periodically measured bone density by dual X-ray absorptiometry.
4. Ascertained fractures for an average follow-up of 7 years (from mean baseline age 62 to age 69).
5. Analysis was by intention-to-treat.

RESULTS

1. At the end of the trial, 76% were still taking some of the study medication; 59% were taking 80% or more.
2. Bone mineral density was greater in the calcium + vitamin D group at year 7 by 1%.
3. Fracture rate overall*

	Ca + D	Placebo
Hip	175	199
Vertebral	181	197
Forearm of wrist	565	557
Total	2102	2158

(*Intention-to-treat. No statistical difference between groups.)

4. Among women who were adherent (ie, took at least 80% of their study medication), C + D supplementation resulted in a 29% reduction in hip fracture—68 in the C + D group vs 99 in the placebo group (95% confidence interval = 0.52-0.97—statistically significant).
5. Adverse effects: kidney stones were reported by 449 women in the C + D group vs 381 in the placebo group. (Hazard ratio = 1.17—statistically significant). [*By my calculation this = one per 500 women over 7 years. RTJ*]

DISCUSSION

1. "The trial demonstrated that calcium with vitamin D supplementation diminishes bone loss at the hip, but the

observed 12 percent reduction in the incidence of hip fracture (the primary outcome) was not statistically significant."

2. There were no significant reductions in incidence of other fractures.
3. The main adverse effect was a small increase in the incidence of renal calculi.
4. It is possible that the results seen in the intention-to-treat analysis might have been due to a too-low dose of vitamin D. The majority of studies supporting a benefit from calcium with vitamin D supplements evaluated vitamin D at doses equivalent to 600 IU or higher.
5. "It is also plausible that there was a benefit only among women who adhere to the study treatment." Only 59% of women were still taking the intended dose of the study medication at the end of the trial.
6. Further analysis, among adherent subjects, indicated that there was an absolute reduction in hip fracture of 1 per 2500 women.
7. The trial was not able to distinguish between effects of calcium and vitamin D.
8. Some support to benefit of C + D is provided by subgroup analyses suggesting that among women over age 60 (who had a higher absolute risk of hip fracture), calcium + D significantly reduced risk of hip fractures. The number needed to treat for one year to prevent one hip fracture among women over age 60 is about 1900.
9. "Although the statistically null primary effect argues against recommending universal calcium with vitamin D supplementation for already calcium replete women, the findings provided evidence of a positive effect of calcium with vitamin D on bone health in older postmenopausal women."

CONCLUSION

"Among healthy postmenopausal women, calcium and vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture."

NEJM February 16, 2006; 354: 669-83 original investigation by the Women's Health Initiative Investigators, first author Rebecca D Jackson, Ohio State University, Columbus.

No Benefit; No Harm

2-5 CONJUGATED EQUINE ESTROGENS AND CORONARY HEART DISEASE:

The Women's Health Study

Recent randomized trials of hormone replacement therapy (**HRT)** with conjugated equine estrogens (CEE) + medroxyprogesterone reported no protection against coronary heart disease **(CHD),** and may have increased risk.[1,2]

This associated, but separate, trial considered women who had experienced a hysterectomy and were eligible to receive unopposed CEE . This is the final report of the trial.

Conclusion: Unopposed CEE was associated with a neutral effect on CHD. (No benefit; no harm.)

STUDY

1. Randomized over 10 000 women (mean age = 64) to; 1) unopposed CEE 0.625 mg daily, or 2) placebo. All women had undergone a hysterectomy. Many had risk factors for CHD—hypertension, diabetes, dyslipidemia, smoking.
2. Followed for 7 years. Primary efficacy outcome = myocardial infarction or coronary death.

RESULTS

1. At the end of the trial, 54% of the women had discontinued use of the study medication.
2. At the end of year 1, the CEE group (compared with the placebo group) had higher HDL-c. lower LDL-c, lower glucose, and lower insulin levels. Their triglyceride levels rose.
3. At 7 years, 201 coronary events occurred in the CEE group, vs 217 in the placebo group. (No clinical or statistical difference.)

DISCUSSION

1. CEE provided no overall protection against CHD. Nor did it result in any harm.
2. The investigators suggest that the difference in CHD risk between the trial of women receiving CEE + progestin vs the present trial could be due to the addition of progestin in the former. The addition of progestin unfavorably affected HDL-c and fibrinogen levels. "Progestin remains a viable explanation for the differences between the trials."
3. "The assumptions and concepts underlying putative coronary protection from postmenopausal hormone therapy have undergone strenuous reconsideration as a consequence of recent randomized trials."

CONCLUSION

CEE used alone over 7 years, provided no overall protection against CHD in generally healthy postmenopausal women. Neither did it provide harm.

Archives Intern Med February 13, 2006; 166: 357-365 Original investigation by The Women's Health Initiative Investigators, first author Judith Hsia, George Washington University, Washington DC

1 JAMA 2002; 288: 321-33

2 NEJM 2003; 349: 523-34

Associated With Significant Deficits in Cognitive Functioning

2-6 NON-DEGENERATIVE MILD COGNITIVE IMPAIRMENT IN ELDERLY PEOPLE AND USE OF ANTICHOLINERGIC DRUGS

Dysfunction of the cholinergic system has a detrimental effect on cognitive performance. The anticholinergic agent, scopolamine, reduces hyppocampal activation, and, when given to young adults, produces cognitive defects characteristic of aging-related changes, rather than dementia.

Drug consumption in elderly people is high. Many commonly prescribed drugs have anticholinergic effects (antiemetics, antispasmodics, bronchodilators, antiarrhythmic drugs, antihistamines, analgesics, antihypertensives, antiparkinsonian agents, corticosteroids, skeletal muscle relaxants, ulcer drugs, and psychotropic drugs). These are likely to have a more toxic effect in an aging brain because of increased permeability of the blood-brain barrier, slower metabolism and drug elimination, and polypharmacy.

Doctors commonly fail to associate cognitive dysfunction in elderly people with anticholinergic agents. They also underestimate anticholinergic toxicity, and prescribe such drugs at high doses. An increasing number of such compounds are available without prescription.

This study tested whether drug-induced anticholinergic burden is associated with cognitive dysfunction.

Conclusion: Elderly people taking anticholinergic drugs had significant deficits in cognitive functioning as compared with non-users. They were likely to be classified as mildly cognitively impaired.

STUDY

1. Randomly selected 372 persons aged over 60 from sixty-three general practices in France. None had senile dementia.
2. Conducted a general health interview to obtain information on current and past illnesses and current depressive symptoms. Determined currently used drugs (prescribed, and without prescription).
3. Quantified anticholinergic burden of the drugs by: 1) serum assays, and 2) the summation of average estimated clinical effects of specific drugs taking into account duration of exposure, It assumed drugs to have additive effects.
4. Constructed, from an extensive literature review, a table of known anticholinergic drugs and their serum anticholinergic activity.
5. Classified anticholinergic burden: 0 = no anticholinergic drug used; 1 = drug used with no likely effect; 2 = drugs used with low effect, and 3 = drug used with high effect.
6. Assessed cognitive performance by neuropsychiatric examination using scores of: reaction time; reasoning; attention; memory; visuospatial ability; and language.
7. Mild cognitive impairment was diagnosed in the presence of a complaint from either the patients or a family member, absence of dementia, a decline in any area of cognitive functioning, with preserved overall general functioning, but possibly with increasing difficulty in performing activities of daily living. Defined the cognitive defect as performance > 1.5 standard deviations below the mean score of the total population at baseline taking into account age and education.
8. Compared cognitive performance of users with non-users of anticholinergic drugs over the past year.

RESULTS

1. Of the 372 subjects, 51 (14%) were taking at least one anticholinergic drug at baseline. (Nine were

taking more than one.) None were taking acetylcholinesterase inhibitors. At the end of the year, 30 of 51 were still taking the drugs regularly.

2. Compared with the non-users, the 30 continuing users had poorer performance on reaction time, attention, memory, visuospatial construction, and language tasks. 80% were classified as having mild cognitive impairment, compared with 35% of non-users.
3. Even after adjustment for confounding variables, participants who used anticholinergic drugs had significantly poorer performance on psychomotor speed, visuospatial memory, narrative recall, and visuospatial construction.
4. No difference in development of dementia at a follow-up of 8 years. Acetylcholinesterase inhibitors would *not* be appropriate therapy in this group of patients. "Longitudinal, population based studies have shown that most people with mild cognitive impairment do *not* develop dementia even after 5 to 10 years of follow-up. "

DISCUSSION

1. "In our sample of elderly people without dementia, we found that those taking anticholinergic drugs showed specific cognitive defects compared with non-users of anticholinergic drugs, and were more likely to be classified as having mild cognitive impairment."
2. The performance of drug users is, in these respects, similar to younger adults given scopolamine.
3. Other factors may be associated with mild cognitive impairment (age—the principal risk; education; treatment for hypertension; and untreated depression).
4. "We found that anticholinergic drug use to be the most significant independent predictor of mild cognitive impairment." People using anticholinergic drugs are highly likely to be included as cases of mild cognitive impairment in population studies, and may represent a fifth of all cases of mild cognitive impairment.
5. Doctors should assess current use of anticholinergic drugs in elderly people before considering administration of acetylcholinesterase inhibitors (eg, donepezil [*Aricept*] used for treatment of dementia of early Alzheimer's disease)

CONCLUSION

Elderly people taking anticholinergic drugs had significant deficits in cognitive functioning and were likely to be classified as mildly cognitively impaired. They did not progress to dementia.

BMJ February 25, 2006; 332: 455-58 Original investigation, first author Marie L Ancelin, Inserm, Pathologies of the Nervous System, Montpellier, France.

Go to http://bmj.com/cgi/doi/10.1136/bmj.38740.439664.DE the full version of the article listing the 27 anticholinergic drugs used by study participants

The list included: four phenothiazines; three anxiolytics; three antiparkinsons; six tricyclic antidepressants; two antihistamines; there antispasmotics. It also included drugs one might not expect to be anticholinergic: digoxin and furosemide. Almost all were "high effect" (class 3) drugs.

Is Melatonin Ineffective?

2-7 EFFICACY AND SAFETY OF EXOGENOUS MELATONIN FOR SECONDARY SLEEP DISORDERS AND SLEEP DISORDERS ACCOMPANYING SLEEP RESTRICTION

Sleep disorders affect about one in every 5 persons in the USA. A disorder is said to exist when a lower quality of sleep leads to impaired functioning or excessive sleepiness.

Secondary sleep disorders are sleep problems associated with medical, neurological, or substance misuse disorders.

Sleep restriction is inadequate sleep resulting from imposed, or self-imposed, lifestyles and work schedules (eg, air travel and shift work).

Complementary and alternative medicines have been used increasingly to manage sleep disorders.

This systematic review assessed efficacy and safety of melatonin for managing secondary sleep disorders and sleep restriction.

Conclusion: No [*statistical*] evidence that melatonin is effective. There is evidence that melatonin is safe with short-term use.

STUDY

1. This meta-analysis included 18 randomized, controlled trials. All trials compared melatonin with placebo.

RESULTS

1. Secondary sleep disorders:
   A. Sleep onset latency (amount of time between lying down to sleep and onset of sleep): Six trials (97 participants) showed no evidence that melatonin had an effect on sleep onset latency. The combined estimate favored melatonin by a mean of 13 minutes. However, the confidence interval was -27 to 0.9 minutes, and thus did not quite reach the 0.05 significance level. Heterogeneity between studies was substantial. When one outlier trial which favored placebo was eliminated, the result became statistically significant (CI = -26 min to – 8 min)
   B. Other efficacy outcomes: Six trials showed a significant effect favoring melatonin. (Weighted mean difference = 1.9%; confidence interval = 0.5 to 3.3) "However, the effect seems not to be clinically important".
2. Sleep restriction:
   A. Sleep onset latency: Nine trials produced a combined estimate that favored melatonin, but was not statistically significant. Mean difference = -1 minute; confidence interval = -2.7 min to 0.3 min.
   B. Other efficacy outcomes: For sleep efficiency (time spent in bed asleep), the combined estimate

from 5 trials showed no statistically significant difference between melatonin and placebo. Weighted mean difference = 0.5%; confidence interval = -0.6% to 1.6%

3. Safety over 3 months or less: The most commonly reported adverse effects were headache, dizziness, nausea, and drowsiness. The occurrence of these outcomes did not differ between groups.

DISCUSSION

1. "Our review showed that melatonin does not have a [*statistically*] significant effect on sleep onset latency in secondary sleep disorders, or sleep disorders accompanying sleep restriction."
2. Melatonin was associated with an increase in sleep efficiency which was statistically significant. The investigators comment that the effect was small (1.9%), an increase of less than 10 minutes in the amount of time spent asleep for eight hours spent in bed. "We consider this effect to be clinically unimportant."
3. There was substantial heterogeneity[1] between studies. The melatonins used varied in quality, formulation, in rate of release, and dose. They also varied in duration of administration.
4. Two other systematic reviews examined the use of melatonin in alleviating the effect of jet lag. Both reported *beneficial* effects.

CONCLUSION

"There is no evidence that melatonin is effective in treating secondary sleep disorders, or sleep disorders accompanying sleep restriction such as jet lag or shiftwork disorder."

BMJ February 18, 2006; 332: 385-88 Original investigation, first author Nina Buscemi, University of Alberta, Edmonton, Canada.

Study funded by the National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda MD.

Melatonin is a hormone secreted by the pineal gland. Its chemical structure is relatively simple—N-acetyl-5-methoxytriptmine, derived from serotonin. Secretion begins in response to waning light. (Melatonin is a "Night-blooming hormone".)

1 The trials were conducted in small groups of subjects. The investigators considered patients with a large range of disorders (eg, dementia, Rett syndrome, neurological impairment, depression, schizophrenia), Melatonin dose ranged from 0.5 mg to 7.5 mg. There was no statement of purity of the substance used. The meta-analysis goes far beyond comparing apples and oranges. It also compares grapes, bananas, pears and pineapples.

Is Melatonin Legal Fiction?

2-8 DOES MELATONIN HELP PEOPLE SLEEP? ***It Is A Misapplied But Probably Safe Miracle Drug***

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

In the USA, melatonin is a popular drug that has the legal status of a "nutritional supplement", although that is "legal fiction". As a result, it is not regulated as a medicine, and is advertised and sold widely—in pharmacies, health food shops and on the internet. Millions of people use it mostly because they believe it will help them sleep.

Claims for melatonin products and their pharmaceutical quality are not controlled. Their safety has not been systematically studied.

In the trials of secondary sleep disorder, melatonin had no significant effect on the time taken to fall asleep and caused a small but unimportant increase in the time in bed spent asleep ("sleep efficiency").

Shift work disorder differs in that the time zone and environments remain the same while people are subjected to new rhythms of sleep and wakefulness. These altered rhythms sometimes continue for long periods and often occur in repeated cycles separated by periods of normal working times. In these circumstances, melatonin secretion does not adapt in the same way and is much less predictable. To lump jet lag and shiftwork disorder together makes no sense. Jet lag is worst during the first two days after arrival and steadily lessens. The time course of symptoms must be tracked accurately and compared at several points. Trials differed in this respect and in the size and timing of doses of melatonin.

The popular misconception underlying the widespread use of melatonin is that it induces sleep pharmacologically. It does not. Melatonin is a regulating switch, pushing the body's circadian phase forward or backward, depending on when it is taken. If taken at the time of darkness, it substitutes for the endogenous secretion which normally starts then. The phase shifts forward, towards the sleep phase. The effect is greater because the doses used are vastly greater than the amount normally secreted. Taking it early in the morning (at the place of arrival) after a long flight eastwards, delays circadian adaptation.

BMJ February 18, 2006; 332: 373-74 Editorial by Andrew Herxheimer, UK Cochrane Centre, London.

Combined G and C May Be Effective In the Subgroup with Moderate-To-Severe Pain.

2-9 GLUCOSAMINE, CHONDROITIN SULFATE, AND THE TWO IN COMBINATION FOR PAINFUL KNEE ARTHRITIS

Glucosamine **(G)** and chondroitin **(C)** are classified as "dietary supplements". They have been advocated (especially by the lay media) as safe and effective options for the management of symptoms of osteoarthritis **(OA)**.

This randomized, double-blind, placebo-controlled trial compared G sulfate, C**,** both, celecoxib, and placebo for 6 months in patients with knee osteoarthritis.

Conclusion: *Overall*, G-alone, C-alone, and both in combination, did not reduce pain effectively. Combined G + C may be effective in the subgroup with moderate-to-severe pain.

STUDY

1. All subjects had knee pain due to OA. Mean age = 58; mean BMI = 32.[1]

2. Randomized over 1500 patients with symptomatic knee osteoarthritis to:
    1) G sulfate-alone 1500 mg daily
    2) C-alone 1200 mg daily
    3) Both daily
    4) Celecoxib 200 mg daily, or
    5) Placebo
2. Assignment was stratified according to severity of pain—mild, and moderate-to-severe. [2]
3. Acetaminophen up to 4000 mg daily was allowed as rescue analgesia.
4. Primary outcome = a 20% decrease in pain from baseline to 24 weeks based on a pain score.
5. Product selection: The study was conducted under an investigational new drug application. As such, C and G were subject to pharmaceutical regulation by the FDA. Ingredients were tested for purity, potency and quality.

RESULTS

1. *Overall*, for all randomized patients, C and G were *not* significantly better than placebo in reducing knee pain by 20%. Change in WOMAC pain score for placebo = -86 points; for G + C = -100 points. *Overall*, the rate of response to placebo was high (60% reported a decrease in pain of 20% or more). As compared with placebo, the rate of response to G was 4% higher. And the rate of response to C was 5% higher. The rate of response to both C and G combined was 10% higher. (Not statistically significant.)
2. *Overall*, response to celecoxib was 10% higher than to placebo. And response time was much faster than for C and G.
3. For patients with moderate-to-severe pain, the rate of response to C + G combined was significantly higher than for placebo (79% vs 54%). Change in *mean* WOMAC pain scores from baseline to end of follow=-up = -123 points in the placebo group vs -153 points in the C + G group. (Statistically significant; p = 0.009) .
4. For patients with moderate-to-severe pain, G +C was associated with a *greater* reduction in pain than celecoxib: - 177 points vs – 153 points.
5. Acetaminophen use at the end of follow-up differed little between groups (from a mean of 1.2 tablets at baseline to 1.8 tablets).
6. Adverse events were mild, infrequent and evenly distributed between groups.

DISCUSSION

1. The “dietary supplements” C and G are widely used for OA. Annual sales exceed $700 million.
2. Analysis of the primary outcome did *not* show that either supplement used alone or in combination was efficacious.
3. In the subgroup with moderate-to-severe pain, G and C combined did significantly (*statistically*) decrease knee pain.
4. Treatment with C was associated with a significant decrease in joint swelling.

5. In the USA, G and C are considered "dietary supplements" and are not held to the stringent standards of pharmaceutical manufacture. "If these agents are to be widely used for the treatment of osteoarthritis, serious consideration must be given to their current regulatory status in order to ensure potency and purity." Other studies have demonstrated substantial variation between the content listed on the label and the actual content. The carefully selected C and G products use in this study are not likely to be available over the counter at the local drug store.

CONCLUSION

Overall, G-alone and C-alone, or both in combination, did not reduce pain effectively in patients with OA of the knee. Analysis suggests that combined G + C may be effective in reducing pain in patients with moderate-to-severe knee pain.

NEJM February 23, 2006; 354: 795-808 The *Glucosamine/Chondroitin Arthritis Intervention Trial* (GAIT), original investigation, first author Daniel O Clegg, University of Utah School of Medicine, Salt Lake City.

Study supported by the National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Washington DC.

1 This says volumes about the cause of OA.

2 The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).The scale of pain on this score ranges from 0 to 500. Overall, the subjects' mean pain score = 235 A score of 125 to 300 was considered to be mild pain; 301 to 400 moderate-to-severe pain.)

An editorial in this issue of NEJM (PP 858-60) by Marc C Hochberg, University of Maryland school of Medicine, Baltimore comments:

Two previous randomized trials reported that 3 years of treatment with G-alone slowed progression of OA of the knee (a structure-modifying effect), and C-alone slowed radiological progression over 2 years. Both are considered to be slow-acting drugs in this respect.

The editorialist comments the study might have been more clinically meaningful for primary care practice, if products obtained off the shelf were used.

A Promising Anticoagulant. Long-Term Efficacy Not Established.

2-10 EFFICACY AND SAFETY OF FONDAPARINUX FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN OLDER ACUTE MEDICAL PATIENTS

"Most patients who die from pulmonary embolism **(PE)** as a complication of being admitted to hospital are medical patients." Around 10% of deaths in medical patients are due to PE.

Fondaparinux (*Arixtra*; Glaxco SmithKline) is a synthetic, selective inhibitor of factor Xa. It effectively reduces postoperative venous thromboembolism **(VTE)** after orthopedic surgery.

This study determined the short-term efficacy and safety of fondaparinux in older, acutely ill *medical* inpatients.

Conclusion: Fondaparinux given for 2 weeks was effective in prevention of VTE in these patients. Frequency of bleeding was similar to placebo.

STUDY

1. Double-blind, randomized trial, placebo-controlled trial followed 839 seriously ill medical inpatients age 60 and over. All had been admitted for congestive heart failure (class III and IV), acute respiratory illness in the presence of chronic lung disease, or acute infectious or inflammatory disorders. All were expected to remain in bed for at least 4 days. The suspected VTE rate in the placebo group = 10% to 14%.
2. Randomized within 48 hours to: 1) fondaparinux, or 2) placebo.. Doses were given subcutaneously daily (2.5 mg fondaparinux or 0.5 mg saline).
3. Treatment was scheduled to continue until days 6 to 14.
4. Primary efficacy outcome = composite of VTE detected by routine bilateral venography + symptomatic VTE *up to day 15*. Secondary outcomes = death and bleeding.
5. Follow-up for one month.

RESULTS

1. Treatment lasted a median of 7 days; 644 patients were available for primary efficacy analysis.
2. Primary efficacy outcome *for first 15 days only*:

	Fondaparinux	Placebo
Any VTE	18	29
Proximal deep vein thrombosis	5	7
Distal deep vein thrombosis	13	22
Fatal PE	0	5
Total	18/321 (5.6%)	34/323 (10.5%)

(NNT to prevent one VTE = 20.)

3. Symptomatic VTE *up to day 32*:

	Fondaparinux	Placebo
Symptomatic deep vein thrombosis	0	0
Non-fatal pulmonary embolism	1	4
Fatal pulmonary embolism	3	7

4. Ten *additional* cases of PE occurred during follow-up after day 15—4 in the fondaparinux group, 6 in the placebo group. Five were fatal (3 in the fondaparinux group).[1]
5. Major bleeding occurred in one patient in each group. (0.2%)
6. Deaths up to one month; fondaparinux 14 (3.3%)' placebo 25 (6%).

DISCUSSION

1. Daily injections of fondaparinux *for 6 to 14 days* reduced the rate of VTE in these older medical inpatients. Consistent reductions were shown in the incidence of total, proximal, and distal deep vein thrombosis.

2. Major bleeding during the first 15 days occurred in one patient in each group. (0.2%) "The reduction in venous thromboembolism was achieved with a minimal risk of major bleeding complications."
3. Results were comparable to reports of efficacy of high-dose low-molecular weight heparin.
4. "These results add to the data supporting the general applicability of fondaparinux in the prevention as well as treatment of venous thromboembolism."
5. Two thirds of the clinically apparent events and half of the fatal PE were observed *after* the initial 6 to 14 day study period. This supports the need to evaluate extended prophylaxis in medical patients.
6. "We believe that our study could best contribute to the improvement of clinical practice if we applied simple and easily generalisable patient selection criteria to general medical inpatients without further risk factor assessment."

BMJ February 11, 2006; 322: 325-27 Original investigation, first author Alexander T Cohen, Guy's, King's, and St. Thomas' School of Medicine, London, UK

Study funded by Sanofi-Synthelabo (France) and NV Organon (Netherlands).

Look For Early Signs Of Sepsis: Leg Pains, Cold Hands and Feet (Despite Fever) , Abnormal Skin Color

2-11 CLINICAL RECOGNITION OF MENINGOCOCCAL DISEASE IN CHILDREN AND ADOLESCENTS

Meningococcal disease **(MD)** is a rapidly progressive infection of global importance. MD is initially misdiagnosed. The infection can progress from initial symptoms to death within hours. Diagnosis must be made as early as possible.

Primary care clinicians see few cases outside the hospital in their lifetime. They may have difficulty in recognizing MD in an early stage.

The diagnosis often depends on textbook descriptions of classic features such as hemorrhagic rash, meningism, and impaired consciousness. These signs appear late in the course of the disease.

Recognition of some early features of sepsis may make the diagnosis promptly.

This study determined the frequency and time of onset of clinical features of MD.

Conclusion: About 75% of children have three early symptoms of MD which may permit early diagnosis.

STUDY

1. Questionnaire obtained data from parents and primary care records for the course of illness before hospital admission in 448 children age 16 and younger with MD. (103 were fatal.)
2. Parents were asked the time of day the initial symptoms began. The questionnaire used a checklist of pre-defined clinical features to record their presence and time of appearance
3. Diagnosis of MD was confirmed with microbiological techniques in 373. The rest were diagnosed by the clinical course which included purpuric rash, meningitis, and/or evidence of septic shock.
4. Calculated the number of hours from the onset of illness to the initial consultation, and to hospital admission

(or to death before admission).

RESULTS

1. Most children had only non-specific symptoms in the first 4 to 6 hours, but were close to death by 24 hours.
2. Classical symptoms of rash, meningism, and impaired consciousness appeared late. (median onset = 13 to 22 hours).
3. Symptoms appearing earliest were common to many self-limiting illnesses seen in primary care. Fever was the first symptom seen in children under age 5; headache the first in the older children. Loss of appetite, nausea, and vomiting were common early features. Many had upper respiratory symptoms.
4. Three quarters of children had early symptoms of sepsis. In all age groups, the first *specific* clinical features were signs of sepsis—leg pain, cold hands and feet, and/or abnormal skin color (pallor or mottling). Most of these symptoms appeared at a median time of 8 hours—before the first medical contact. This was much earlier than the median time to hospital admission (19 hours).
5. Rash was the first *classical* symptom to emerge. At onset, the rash was often non-specific. It developed into a petechial or large hemorrhagic rash over several hours. The close correspondence of the median time of onset of rash and the first medical contact was unlikely to be coincidental. (The importance of a non-blanching rash is the central message of most public education campaigns about MD.)
7. The median time to onset of specific meningitis symptoms (neck stiffness, photophobia, bulging fontanelles) was around 12-15 hours. Unconsciousness, delirium, seizures occurred later.
8. Few children developed any new symptoms after 24 hours.

DISCUSSION

1. “We have identified three important clinical features—leg pain, cold hands and feet, and abnormal skin colour—that are signs of early meningococcal disease in children and adolescents.” These features generally occur within the first 12 hours of the onset of illness, and are often present at the first consultation with a primary care physician.
2. Cold hands and feet, and abnormal skin color are features of early sepsis. They represent change in the peripheral circulation. Leg pain is less well recognized, although pain in the limbs with and without refusal to walk, has been reported in children with septicemia. The presence of these features also suggests that vital signs (pulse, respiratory rate, and capillary return) might also be abnormal.
3. MD can rarely be excluded by clinical examination in the first 4 to 6 hours of illness.. If the child has MD, symptoms will progress rapidly after a period of a few hours. If there is doubt, a second consultation should be scheduled within the next 4-6 hours.
4. The classical symptoms of MD appear later.
5. “We believe our evidence is sufficiently robust to argue that we need a diagnostic paradigm shift.”

CONCLUSION

Classical clinical features of MD appear late in the illness. Recognizing early symptoms of sepsis could increase the proportion of children identified promptly.

Lancet February 4, 2006; 367: 397-403 Original investigation, first author Matthew J Thompson, University of Oxford, UK.

Does a High Intake of Chocolate Reduce Risk of Death?

2-12 COCOA INTAKE, BLOOD PRESSURE, AND CARDIOVASCULAR MORTALITY

Cocoa has a rich history, covering a period of over more than 2600 years. In ancient history, numerous positive properties to health were ascribed to cocoa and chocolate.

Cocoa is a rich source of flavanols. Previous small randomized trials have reported beneficial effects of cocoa in improving endothelial function, lowering BP, and lowering risk of cardiovascular disease **(CVD).** Most previous trials used cocoa that contained much higher amounts of flavanols than commercially available products.

This study estimated intake of cocoa from the habitual consumption of cocoa-containing foods, and evaluated whether intake was inversely related to BP and CVD and all-cause mortality in a cohort of elderly men.

Conclusion: In this cohort of elderly men living in Zutphen, Netherlands, intake of cocoa was inversely related to BP, and was associated with a lowering cardiovascular and all-cause mortality.

STUDY

1. Used data of 470 elderly men (mean age at baseline = 72). All were free of chronic diseases at baseline (1985).
2. Measured BP at baseline and 5 years later.
3. Assessed habitual food consumption by dietary history at 5-year intervals. This included consumption of cocoa-containing foods. Chocolate confectionary contributed about 2/3 of the total cocoa intake.
4. Ascertained causes of death during 15 years of follow-up.

RESULTS

1. Mean blood pressure highest tertile of cocoa use vs lowest tertile of use:
   A. Mean systolic was 3.7 mmHg lower.
   B. Mean diastolic was 2.1 mmHg lower.
2. Death during follow-up (n = 314 of 470; 152 died of cardiovascular diseases):
3.

	Tertiles of cocoa intake		
	Lowest (0.5 g/d)	Middle (0.5-2.25 g/d)	Highest (> 2.3 g/d)
No of subjects	165	149	156
Cocoa median g/d	0	0.92	4.2
Cardiovascular mortality	58 (36%)	50 (34%)	44 (27%)
/1000 person years	39	31	24
RR after adjustments	1.00	0.79	0.50*

All-cause mortality	122 (76%)	100 (68%)	92 (57%)
/1000 person years	82	64	50
RR after adjustments	1.00	0.80	0.53*

4. Relative risk of death:

A Cardiovascular death (CVD): highest tertile compared with lowest tertile of cocoa use = 0.50.

B. All-cause mortality: highest tertile vs lowest tertile of cocoa use = 0.53.

(These RRs resulted from a model which adjusted for 19 possible confounders. RTJ)*

DISCUSSION

1. "In the present study, usual daily cocoa intake was inversely related to blood pressure."
2. "In prospective analysis, usual cocoa intake was associated with a 45% to 50% lower risk of cardiovascular and all-cause death."
3. "A major concern in observational studies is the possibility of residual confounding." In this study, cocoa users consumed less meat and coffee, and consumed more dairy, sugar, and cookies, and were more likely to use alcoholic drinks.
4. There was no association between cocoa intake and BMI.
5. The present study indicates that men with a usual cocoa intake of about 4.2 g, equal to 10 g of dark chocolate per day had a lower BP.
6. The lower cardiovascular mortality could not be attributed to the lower BP. "Our findings suggest that the lower cardiovascular mortality related to cocoa intake is mediated by mechanisms other than lowering blood pressure."
7. Other studies have suggested that cocoa intake improves endothelial function, reduces fasting insulin and glucose levels (dark chocolate), and inhibits platelet function.
8. Before drawing conclusions, confirmation by other observational and experimental studies is needed."

CONCLUSION

In this cohort of elderly men, cocoa intake is inversely associated with blood pressure and 15-year mortality.

Archives Intern Med February 27, 2006; 166: 411-177 original investigation, first author Brian Buijsse, National Institute for Public Health and the Environment, Bilthoven, Netherlands.