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DIET DRUGS AND PULMONARY HYPERTENSION

Reference Abenhaim L, Moride Y, Brenot F, Rich S, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335:609-16.

Clinical question **Does the use of appetite-suppressant drugs, including the newly FDA-approved agent dexfenfluramine, increase the risk of primary pulmonary hypertension?**

Background Primary pulmonary hypertension (PPH) is a poorly understood, rare disorder that is often irreversibly fatal. Its peak incidence appears to be among women in their 30s and 40s. In the early 1990s, French researchers identified a cluster of PPH cases among patients who had used derivatives of the anorexic agent fenfluramine. The current study tries to establish whether users of appetite-suppressant agents, including dexfenfluramine, have an increased risk of developing PPH.

Population studied Ninety-five PPH cases from France, Belgium, the UK, and the Netherlands were identified prospectively at 220 cardiology and pulmonary medicine centers in those countries between 1992 and 1994. The patients ranged in age from 18 to 70 years, with a mean of 44; the ratio of women to men was 2.3:1. The patients were free of any other chronic active life-threatening disease, and those with pulmonary hypertension from obvious causes such as chronic obstructive pulmonary disease, pulmonary embolism, congenital heart and lung defects, and central hypoventilation were excluded.

The diagnosis was established by right heart catheterization, which showed a mean PA pressure of 57 among the case patients (normal is about 15), buttressed by results from perfusion lung scans, echocardiography, chest x-rays, and arterial blood gases. The case patients were compared with 355 controls, matched for variables including age, sex, and area in which they lived.

Study design and validity The investigators used a prospective case-control design. Patients and controls were questioned by trained interviewers with no medical background who were blinded to the purpose of the study. From each patient and control, the interviewers took a medical history and a detailed drug use history. Among the anorexic agents tabulated were fenfluramine and dexfenfluramine; several amphetamine-like agents; and any compounds that included anorexic agents and other appetite-suppressant medications. Odds ratios were calculated by conditional logistic regression to account for obesity-related confounding variables and other possible risk factors.

Outcomes measured The main outcome measured was the likelihood of PPH among patients using anorexic drugs compared with patients who did not use such drugs.

Results Of the 95 case patients, 30 (31.6%) had previously used anorexic agents, compared with 26 of 355 controls (7.3 %), producing an adjusted odds ratio (OR) of 6.3 (95% CI, 3.0 to 13.2). Fenfluramine and dexfenfluramine were used by 22 of the case patients and 23 of the controls. Among those who used anorexic agents, the risk of developing PPH was highest among those who had used anorexic agents in the year prior to diagnosis (OR 10.1, 95% CI, 3.4 to 29.9). It was also much higher for those using the drugs longer than 3 months (OR 23.1, 95% CI, 6.9 to 77.7) compared with those using them for no more than 3 months (OR 1.8, 95% CI, 0.5 to 5.7).

Recommendations for clinical practice **Dexfenfluramine leads the pack of appetite-suppressant agents effective for short-term weight loss among severely obese patients with a body mass index of at least 30. The risk of PPH among users of anorexic agents is significantly elevated, but the absolute incidence is still small: 28 cases per million person-years of exposure, comparable to the fatality risk from penicillin-caused anaphylaxis.[1] Clinicians prescribing these medications should weigh the risks posed by the patient's obesity versus the risk of inducing PPH; an accompanying editorial argues that the risk of death from untreated obesity is perhaps 20 times higher than the estimated mortality from PPH among patients given appetite-suppressant drugs.[1]**

Patients treated should be on a diet and exercise regimen, and closely monitored for new-onset fatigue, dyspnea, chest pain, syncope, or edema. Those who do not show significant weight loss

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within the first month of therapy should have the drug stopped. Caution should be used in prescribing the drugs for longer than 3 months. It remains unclear which subsets of patients are at highest risk and what are optimal monitoring measures and their frequency.

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The Effect of First-Contact Care on Ambulatory Health Care Expenditures

Reference Forrest CB, Starfield B. The effect of first-contact care with primary care clinicians on ambulatory health care expenditures. J Fam Pract 1996; 43:40-8.

Clinical question **Are health care costs reduced when primary care clinicians provide first-contact care?**

Background Managed care companies and other third-party payers are increasingly cognizant of the cost-effective care provided by primary care clinicians, forming the rationale for the "gatekeeper" models adopted by many organizations. While a growing body of research has demonstrated the magnitude of this cost-effectiveness over a wide variety of conditions, few studies have investigated the underlying mechanisms or explanations.[1-3] This study was designed to investigate the effects of first-contact care provided by primary care clinicians.

Population studied Data were obtained from the National Medical Expenditure Survey (NMES), based on a representative sample of noninstitutionalized persons in the United States in 1987, a time when there were few "gatekeepers" and most Americans had relatively unrestricted access to all aspects of the health care system. There were 19,835 NMES respondents (68.1% of the total sample) who were selected for this study because they could identify a specific primary care clinician in a community-based site (ie, not in a hospital clinic or emergency department).

Study design and validity A complex process was used to identify "episodes of care" from the NMES data. Ambulatory encounters were first grouped into diagnostic clusters. Of the 92 clusters, 24 were selected based on their frequent occurrence, expected duration of less than 3 months, and the expectation that they could be treated without hospitalization. Encounters for the same diagnostic category occurring within a prespecified period were then grouped into "episodes of care" using prespecified decision rules. The episodes identified represented one third of the ambulatory utilization of the study population.

Costs for each episode were calculated from NMES data, and included charges for physician, facility, laboratory, and radiography fees, but did not include any inpatient or pharmaceutical expenses. Multivariate linear regression was used to adjust the findings for factors likely to have an impact on costs, including patient demographics, comorbidity (such as the presence of chronic illnesses), and global health status.

Results First-contact use of the primary care clinician occurred in 49% of episodes, and was associated with large cost reductions; 53% for all types of episodes, 62% for acute illnesses, and 20% for preventive episodes. Episodes beginning with a visit to the primary care clinician were resolved with fewer visits, and with less chance of a subsequent emergency department (ED) visit. Those episodes beginning with a visit to the ED were approximately four times more expensive, but only 9% of episodes involved any ED use. The major effect on cost reduction resulted from the use of fewer resources and decreased expenditures per visit. Adjustment for patient demographics, comorbidity, and health status had little effect, suggesting that these factors were not important determinants of the expenditure differences. The findings were consistent across 23 of the 24 types of episode. Because the data collection occurred in 1987, it is likely that the decreased costs are due to the practice patterns of the primary physicians, rather than to any denial of access to services.

Recommendations for clinical practice **The availability of the patient's usual primary care clinician at the onset of an illness episode leads to decreased health care expenditures. In a related article, Medicare costs were found to be inversely associated with the supply of family physicians.[4] Health care planners and administrators should apply these findings by designing systems in which patients are encouraged to identify a primary care clinician who will provide first-contact care. Family physicians should continue their efforts at providing cost-effective first-contact care.**

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Efficacy of Oral Dexamethasone for Outpatient Croup

Reference Geelhoed GC, Turner J, Macdonald WBG. Efficacy of a small single dose of oral dexamethasone for outpatient croup: a double blind placebo controlled clinical trial. BMJ 1996; 313:140-2.

Clinical question **Can a single oral dose of dexamethasone (0.15 mg/kg) administered to children with mild croup reduce the need for follow-up medical care?**

Background Corticosteroids are now often used for children with severe croup requiring hospitalization. There has been only one study, however, investigating the benefit of steroid treatment in children with croup not requiring hospitalization. In that trial, treatment with intramuscular dexamethasone (0.6 mg/kg) reduced the severity of illness in the first 24 hours, but there was no significant reduction in the need for follow-up care. Oral dexamethasone may be better accepted by both patients and clinicians, and is more available in nonemergent outpatient settings.

Population studied The study population consisted of 100 children, aged 4 months to 10 years, who presented to the emergency department of an Australian children's hospital with a diagnosis of croup not severe enough to require hospitalization. Exclusion criteria included treatment with steroids within the previous week, a preexisting upper airway condition, a history of prolonged stridor, and a questionable diagnosis of croup. Children from families with limited English or without telephones were also excluded.

Study design and validity Eligible children were randomized in a double-blind fashion to receive either oral dexamethasone (0.15 mg/kg) or placebo. Baseline characteristics of the two groups were similar regarding age, sex, and clinical measures of the severity of croup symptoms (heart rate, respiratory rate, pulse oximetry, and a croup score based on degree of stridor and retractions). Outcomes were assessed by a follow-up phone call 7 to 10 days after discharge. No follow-up was obtained from two children in each group. Children not enrolled because of parental request showed no differences in baseline characteristics from the study population.

Outcomes measured The primary outcome measured was the number of children who subsequently attended any medical facility for additional treatment of croup. Other outcomes measured included hospital admissions, duration of croup and other viral symptoms, and whether children sought medical care for other reasons.

Results Eight of the 48 children (16.7%) from the placebo group vs none of the children treated with dexamethasone returned to a medical facility for further treatment of croup ($P<.01$). There were no significant differences between the groups in hospital admissions for ongoing croup, duration of croup or other viral symptoms, and the proportion returning for medical care for reasons other than croup.

Recommendations for clinical practice **In this trial a single oral dose of dexamethasone (0.15 mg/kg) significantly reduced the number of children with mild croup who reattended a medical facility for ongoing croup. The benefits of oral steroids in the outpatient treatment of acute exacerbations of asthma are well accepted. Although usually self-limiting, the stridor and dyspnea of croup may be just as frightening as severe asthma to the parents and child. Since it is inexpensive, easy to administer, and available in any outpatient facility, oral dexamethasone is recommended for children over 3 months of age with mild to moderate croup not requiring hospitalization.**

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Patient Satisfaction with Antibiotic Use

Reference Hamm RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections: are patients more satisfied when expectations are met? J Fam Pract 1996; 43:56-62.

Clinical question **Are patients with common respiratory infections more satisfied when their expectations for antibiotic treatment are met?**

Background It is often difficult for clinicians to distinguish, on clinical grounds alone, common respiratory infections of viral origin from those caused by bacteria. The decision to prescribe antibiotics is a difficult one, influenced by a number of factors other than the clinical picture. This study examines patients' expectations for antibiotics, physicians' perception of those expectations, and the impact of antibiotic prescriptions on

patient satisfaction.

Population studied Patients studied included those presenting with a respiratory infection at two community practices and one academic family practice clinic, representing the collective practices of 13 physicians. Of the 142 patients initially enrolled, 113 patients (80%) and their physicians completed all aspects of the study. Dropouts were primarily the result of an inability to reach the respondent for a follow-up phone interview.

Study design and validity Patients enrolled in this descriptive study completed a previsit questionnaire designed to elicit their expectations for antibiotics, and whether they believed antibiotics kill viruses. They also completed a postvisit questionnaire that asked the latter question again together with questions about satisfaction with their visit. Physicians completed a postvisit questionnaire that asked for their perception of the patient's expectations for antibiotics, the patient's diagnosis, the prescription given, if any, and the rationale behind it. Study participants were not randomly selected but chosen at the discretion of the staff at each clinic. Exactly how patients qualified based on their symptomatology, and who made this determination are unknown. Antibiotic-prescribing practices certainly vary considerably from physician to physician, and are also a function of patient age and predisposing illnesses. These variables are not accounted for in this study.

Outcomes measured Main outcomes measured included the number of patients who expected antibiotics, the number who actually received them, and the number who were satisfied with their visit. The number of patients in whom physicians perceived an expectation for antibiotics was also measured.

Results The previsit questionnaire revealed that 65% of patients expected antibiotics. Sixty-three percent of patients received them. The vast majority of patients (97%) agreed or strongly agreed that they were satisfied with their visit. Factors that did *not* influence satisfaction included whether the patients thought antibiotics were necessary for their illness, whether they received antibiotics, and whether they received what they expected. Measures that had the strongest positive association with patient satisfaction were whether the physician spent enough time explaining the illness and whether the patient understood the physician's choice of treatment.

A perceived expectation for antibiotics was noted by physicians in one half of the patient encounters. There was a large degree of inaccuracy, however, in the physicians' perception of the patients' desire for antibiotics. Eight percent of the physicians who prescribed an antibiotic indicated doing so only because of the patient's desire. One fourth of the infections were documented as upper respiratory viral infections and one fifth of these were treated with antibiotics.

Recommendations for clinical practice **The questions of which factors influence physicians to prescribe antibiotics and whether such prescriptions contribute to patient satisfaction are certainly worthy of study. Unfortunately, because of methodological concerns, no firm conclusions can be drawn from this study. Physicians frequently prescribe antibiotics for upper respiratory viral infections when they believe patients expect it. Receiving a prescription for an antibiotic was not associated with increased patient satisfaction.**

The author's general recommendation, that physicians spend time explaining the nature of a particular illness and their choice of treatment rather than relying on antibiotic prescriptions to generate satisfaction, is applicable and, in an era of increasing antibiotic resistance, is safer and would find few critics.

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Postmenopausal Hormone Therapy and Cardiovascular Risk

Reference Grodstein F, Stampfer M, Manson J, Colditz G, Willett W, Rosner B, Speizer F, Hennekens C. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med 1996; 335:453-61.

Clinical question **Does the addition of progestin affect the risk of cardiovascular disease in women receiving postmenopausal hormone replacement therapy (HRT)?**

Background Combined estrogen and progestin therapy has become the standard treatment regimen for women on postmenopausal HRT. Unopposed estrogen is an acceptable alternative in women who have undergone prior hysterectomy, since the concern of endometrial cancer is eliminated. While the evidence is good that that estrogen therapy in postmenopausal women decreases the risk of cardiovascular disease, comparable data on combination HRT are limited. This study was designed to evaluate the relationship between combination HRT and the risk of cardiovascular disease.

Population studied The study population was 59,337 female nurses aged 30 to 55 years at baseline. Women were classified as postmenopausal from the

time of either natural menopause or a hysterectomy with a bilateral oophorectomy. A total of 662,891 person-years were accrued from 1976 to 1992. Women who reported a history of stroke, myocardial infarction, angina, or cancer were excluded from the study, since these conditions might have caused them to alter their hormone use.

Study design and validity Longitudinal data were obtained by biennial mailed questionnaires for over 90% of the cohort. Initial data points included the subjects' medical history and their use of postmenopausal hormones. Later updates added information on the type of HRT and the estrogen dose. The study followed women for 16 years of postmenopausal HRT to assess the relative risk of cardiovascular disease among women in various categories of hormone use as compared with women who never used hormones. Reported events were verified by review of medical records or death certificates, or by communication with surviving family members. Proportional-hazard models were used to calculate relative risks, adjusted for patient age, age at menopause, body mass index, and a variety of known risk factors for cardiovascular disease.

In a longitudinal cohort study where patients are not randomized to treatment and control groups, it is important that researchers identify and adjust for differences between groups. As noted above, the analysis adjusted for the fact that women who use HRT tend to have a better coronary risk profile than women who do not use HRT. They also adjusted for differences in the age distribution of users and nonusers. Although the authors acknowledged that some unknown confounding variable may play a role in the observed differences, their analysis leaves the range of potential confounders quite narrow.

Outcomes measured The relative risk (RR) of cardiovascular disease (nonfatal myocardial infarction, fatal coronary disease, coronary bypass surgery or angioplasty, and fatal or nonfatal stroke) among women using combination HRT compared with those who used estrogen only or no HRT.

Results A marked decrease in the risk of major coronary disease was observed among women who took estrogen with progestin, as compared with the risk among women who did not use hormones (adjusted RR 0.39; 95% CI, 0.19 to 0.78) or used estrogen alone (adjusted RR 0.60; 95% CI, 0.43 to 0.83). However, there was no significant association between stroke and the use of combined hormones (adjusted RR 1.09; 95% CI, 0.66 to 1.80) or estrogen alone (adjusted RR 1.27; 95% CI, 0.95 to 1.69), although there was some suggestion of an increased risk of stroke in the subgroup of women taking the highest doses of oral conjugated estrogen. The associations were unrelated to the duration of hormone use, and the protective benefit diminished somewhat 3 years after cessation of HRT.

Recommendations for clinical practice **When considering postmenopausal HRT, the combined potential benefits of estrogen (eg, symptom control, decreased risk of osteoporosis, and decreased risk of cardiovascular disease) must be weighed against its potential risks (eg, symptomatic side effects, increased risk of endometrial cancer, and a possible increase in the risk of breast cancer and stroke). The addition of progestin decreases the risk of endometrial cancer, but it has also been demonstrated to attenuate the estrogen-induced elevation of HDL cholesterol. This prospective study concludes that the addition of progestin to postmenopausal HRT does not attenuate the cardioprotective effect of estrogen in relatively young postmenopausal women. Clinicians can integrate this additional information when counseling postmenopausal patients regarding HRT and when formulating their treatment recommendations, with the broader goal of enabling their patients to make more informed health care decisions.**

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Pain Relief for Renal Colic

Reference Cordell WH, Wright SW, Wolfson AB, et al. Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. Ann Emerg Med 1996; 28:151-8.

Clinical question **What is the most effective treatment for pain from renal colic?**

Background Nearly 60% of patients in the emergency department with nephrolithiasis complain of severe pain.[1] While opiates are typically prescribed, previous research (mostly in Europe) has found that NSAIDS are at least as good if not better for pain control.

Population studied Subject patients were recruited at four US urban, tertiary care teaching hospitals. Adult emergency department patients were eligible if their history and physical examination findings were compatible with renal colic, their pain was of moderate to severe intensity, and they had no contraindication to the study drugs. Subjects with any analgesia in the preceding 3 hours were excluded.

Patients were included in the efficacy analysis only if the diagnosis of nephrolithiasis was confirmed by IVP,

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sonography, stone passage, or stone recovery during surgery. A total of 106 patients were available for analysis of the efficacy of the drugs for pain control, and 154 were available for the analysis of adverse effects.

Study design and validity Both patients and physicians were blinded to the choice of medication, and patients were randomized into one of three treatment groups. On entrance to the study one group was given IV ketorolac (60 mg) and placebo, a second group received IV meperidine (50 mg) and placebo, and the third group was given IV ketorolac (60 mg) and IV meperidine (50 mg). Subjects with inadequate pain relief at 30 minutes were given supplemental IV meperidine as needed. Additional ketorolac was not used.

Because patients were recruited over 21 months, it is surprising that only 154 persons were enrolled from the four emergency departments. Additional analysis comparing the subjects with the nonenrolled patients would help us assess whether preferential selection of a subset of patients influences the findings.

Outcomes measured Subjects rated pain intensity on both a visual analog scale and a categorical scale at baseline and 15 and 30 minutes, and 1, 2, 3, 4, 5 and 6 hours after receiving the study drug.

Results There were no significant differences among the three treatment groups for demographic characteristics, baseline pain scores, or concomitant therapies. Patients receiving IV ketorolac experienced faster and better pain relief over the first 30 minutes than did patients receiving meperidine alone. Patients receiving both drugs had pain relief similar to ketorolac alone. Subjects randomized on intake to ketorolac only continued to experience better pain relief for the duration of the 6-hour period and required a mean of 56.9 mg of supplemental meperidine. Patients in the meperidine-only group required a mean of 102.9 mg of supplemental meperidine after the first IV bolus and had significantly poorer pain control over the entire duration of the study. Patients randomized to the combination therapy had pain relief similar to those in the ketorolac-only group, and these two groups used similar amounts of supplemental meperidine. Patients in the combination group had the highest rate of adverse effects and those in the ketorolac group had the lowest rate. No adverse effect was life-threatening and the most common complaints were dizziness and somnolence.

Recommendations for clinical practice **Ketorolac gives better pain relief than meperidine in the setting of renal colic. In addition, not only was the pain relief better, but the side effects were fewer. Although this study used a nonapproved dosage of ketorolac (60 mg), the flat dose-response curve of ketorolac suggests that 30 mg IV should show similar pain relief. This confidence is bolstered by the many other studies that have found better relief of renal colic pain with NSAIDS compared with opiates despite using many different drugs, dosages, and routes of administration.**

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Patient Reassurance When Test Results Are Normal

Reference McDonald IG, Daly J, Jelinek VM, Panetta F, Gutman JM. Opening Pandora's box: the unpredictability of reassurance by a normal test result. BMJ 1996; 313:329-32.

Clinical question **Is a normal test result enough to reassure patients that "nothing is wrong"?**

Background The daily practice of medicine involves searching for disease: case finding. Questionable symptoms or signs (eg, systolic murmur) may be discovered. The diagnostic cascade of specialty referral or test ordering (eg, echocardiogram) begins in an attempt to discriminate between normal and abnormal. Once disease is ruled out, the task turns to reassurance, an outcome of great interest to patients. Unfortunately, little evidence is available to guide clinicians in predicting the success of this endeavor.

Population studied Six university-affiliated cardiologists in Australia were asked to recruit up to 10 consecutive patients who had been referred to exclude heart disease. Forty patients, aged 3 to 74 years, were identified, including 15 female and 25 male patients. Thirty of these patients were asymptomatic and had been referred for evaluation of a systolic murmur detected during a routine examination. Symptomatic patients were being evaluated for palpitations and chest pain.

Study design and validity This descriptive case series evaluated the disease anxiety level before and after an echocardiogram. A cardiologist interviewed each patient following a defined questionnaire. Pretest probability of cardiac normalcy was estimated, and the patient's pre- and posttest anxiety was graded. All patients underwent echocardiography and two posttest home interviews, one as soon as possible

and the second 9 to 12 months later. One patient was unavailable for the immediate home interview, and 4 were unavailable for the follow-up 9 to 12 months later. Because of the small sample size and uncertain selection criteria, results may not be applicable to patients seen by family physicians.

Outcomes measured The primary outcome was the impact of a normal echocardiogram on the patient's level of anxiety concerning heart disease. Patient recall, residual understanding, and uncertainty about test results were also evaluated.

Results The pretest probability of cardiac normalcy was estimated as "certainly normal" in 15 patients, "almost normal" in 16, and "probably normal" in 9 patients. The cardiac echo was normal in 37 of the 40 patients; only 1 patient had a significant abnormality (bicuspid aorta). Thirty-eight patients were included in the final evaluation even though it was stated that 4 were unavailable for long-term follow-up. Thirty of these 38 patients had pretest anxiety, including all 10 symptomatic patients. Twenty-one patients had no anxiety specifically about heart disease until a murmur was discovered. Of the 20 asymptomatic patients with pretest anxiety, 55% reported residual anxiety. Of the symptomatic patients, all had residual anxiety despite the normal echo and consultation. Residual anxiety was inversely proportional to posttest understanding. Overall, anxiety decreased in most patients after the consultation. Patient recall of the consultation was deemed "remarkably accurate."

Recommendations for clinical practice **Patients frequently are not reassured by a normal test result, and once anxiety develops, it may be difficult to completely eliminate. Asymptomatic patients presenting to family physicians are subjected to many tests, including cardiac auscultation, which may have relatively poor sensitivity and specificity for disease, depending on the skill level of the examiner. The resultant posttest probability of disease (how concerned we are that the patient has a disease) may be inappropriately high secondary to a false-positive test interpretation. Unfortunately, cardiac auscultation skills are poorly taught in the medical education process, and rarely improve over that of third-year medical students.[1] It is therefore important for us to enhance our clinical skills and adequately address a patient's understanding of the findings. It is to be hoped that we will be able to minimize unnecessary diagnostic evaluations and adequately prepare our patients for necessary consultations. As B. Lewis Barnett, Jr, MD, reminds us, "While I was listening to your heart . . . I realized how important it was that your heart work right, and how important it was for me to discern as best I could."[2]**

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Screening for Mild Thyroid Failure

Reference Danese MD, Powe NR, Sawin CT, Landenson PW. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. JAMA 1996; 276: 285-92.

Clinical question **Is periodic screening for mild thyroid failure by measuring serum thyroid stimulating hormone (TSH) cost-effective?**

Background Screening for subclinical hypothyroidism, defined as an elevated serum TSH with a normal serum free thyroxine (T_4), may be beneficial for three reasons: (1) to prevent the progression to overt hypothyroidism, (2) to reduce elevated serum cholesterol and related risks by treating mild hypothyroidism, and (3) to reduce the utilization of medical care by patients with unrecognized symptoms. Currently, no health care organization or preventive task force recommends routine periodic screening for hypothyroidism. There have been no randomized clinical trials done to evaluate the efficacy or cost-effectiveness of screening for subclinical thyroid disease.

Population studied and data sources A hypothetical cohort of women and men was screened every 5 years during recommended periodic examinations, beginning at age 35 years. The prevalence of mild hypothyroidism increases with age and is higher in women (4% to 17%) than in men (2% to 7%). The data for men were sparse, so estimates reflect antibody titer reports rather than actual prevalence of disease.

Estimates of the likelihood of progression from hypothyroidism to secondary effects such as myocardial infarction or cerebral vascular disease were based on previous population surveys, reported 10-year follow-up studies of euthyroid women who progressed to hypothyroidism, reported reductions of cholesterol in treated populations who were hypothyroid, and uncon-

trolled studies showing improvement in psychological and neurological symptoms after treatment with levothyroxine sodium in mild thyroid failure. The likelihood of progression to active vascular disease was based on the 18-year and 30-year follow-ups of the Framingham Study.

Costs were taken from Medicare reimbursement rates for November 1994 in Baltimore, Maryland, of typical visits for diagnosis and follow-up. A weighted average of cost was utilized for levothyroxine and lipid-lowering therapy. Costs for adverse events were not included in the model. Published costs for vascular disease were referenced. The quality of life estimates were based on the utility model for health states with a range of 0 (death) to 1 (optimal health). Overt hypothyroidism was 0.17; mild hypothyroidism with symptoms was 0.90.

Study design and validity A Markov tree was constructed that compared screening with TSH and treatment versus no screening until overt symptoms of hypothyroidism (a Markov tree assumes that patients move between health states such as no disease, mild disease, and severe disease at a fixed rate, and is especially appropriate for modeling chronic disease or screening programs). The base-case analysis started screening patients every 5 years at age 35 years and followed them for 40 years. Sensitivity analyses were performed by varying the estimates for factors, and separate models were run for men and women.

Outcomes measured The cost per quality-adjusted life year (QALY) was calculated; costs were discounted to reflect most patients' preference for an immediate benefit rather than a future benefit.

Results The cost-effectiveness of screening 35-year-old patients with a serum TSH assay every 5 years was $9,223 per QALY for women and $22,595 per QALY for men. The cost-effectiveness increased with age for both women and men, and was most favorable for older women (<$5,000 per QALY). The time interval between screening was most cost-effective between 3 and 4 years. As the cost of the TSH assay varied from $10 to $50, the cost per QALY increased from $3,974 to $17,998. As the utility of hypothyroidism with symptoms varied from 0.8 to 1.0, the cost per QALY varied from $6,370 to $16,885. These results are comparable to other standard preventive health screening and treatment modalities such as hypertension ($18,323 per QALY for men and $26,130 per QALY for women).

Recommendations for clinical practice **The advantage of a decision analysis is that it is "explicit, quantitative, and prescriptive." This study leads to the conclusion that screening is not only efficacious in detecting disease but also has cost-effective utility. The disadvantage of a decision analysis is that it may be too "explicit, quantitative, and prescriptive." Should we base complete population screening on assumptions from explicit probability estimates from surveys, single cohort reports, rare estimates, and cost projections? Most task forces require at least one properly designed randomized controlled trial before concluding there is "good" evidence to recommend a screening measure be added to the periodic health examination. This study generates a hypothesis that should be tested in a well-designed clinical trial, especially in older women. Until that time, it would be prudent to limit screening to women who have hyperlipidemia.**

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