POEMs

Patient-Oriented Evidence that Matters

Each month, the POEMs editorial team reviews more than 80 journals of interest to primary care physicians, identifying the articles you have to know about to stay up to date. We call these articles POEMs (Patient-Oriented Evidence that Matters) because they deal with common primary care problems, report outcomes that matter to patients, and have the potential to change the way we practice. The eight most important articles are critically appraised each month by a team of more than 50 reviewers who make a recommendation for clinical practice. The collected reviews of the POEMs are available at the Journal's *World Wide Web site at http://jfp.msu.edu. Additional POEMs and other related evidence-based material are published in a monthly newsletter called* Evidence-Based Practice, *available through subscription (1-800-451-3794; fax 1-203-406-4603) or via the Web site at http://jfp.msu.edu/ebp.htm*

Dietary Soy and Hot Flushes

Albertazzi P, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. Obstet Gynecol 1998; 91:6-11.

Clinical question **Does dietary soy protein reduce the number of hot flushes in postmenopausal women?**

Background Traditional hormone replacement therapy (HRT) is effective for controlling vasomotor symptoms and reducing the risk of cardiovascular disease and osteoporosis in postmenopausal women. Despite these beneficial effects, 85% of postmenopausal women in the US currently do not use any form of HRT. Reasons for the limited use of HRT include concerns about side effects and breast cancer risk, and a desire for a more natural approach to the management of menopausal symptoms. Epidemiologic studies have demonstrated lower rates of breast cancer, heart disease, and osteoporosis in populations of Asian women. The high dietary intake of phytoestrogens, plant substances structurally or functionally related to estradiol and found in high concentrations in soy products, has been postulated as one factor responsible for the reduced rates of disease.

Population studied The authors studied 104 postmenopausal women between the ages of 45 and 62 years requesting treatment for severe hot flushes at two university centers in Italy. To be eligible for the study, patients must have had no menses for at least 6 months, a minimum of seven moderate to severe hot flushes or night sweats per 24 hours over the past 2 weeks, no use of HRT or other medications for at least 6 weeks, an elevated FSH (>50 IU/L), and low serum estradiol concentration (<35 pg/mL).

Study design and validity This is a randomized, double-blinded, placebo-controlled trial of the effect of a soy protein supplement on hot flushes. Fifty-one patients took 60 g of isolated soy protein daily and 53 patients took 60 g of placebo (casein) daily in the form of powdered packets. Patients were seen at the screening visit, 4 weeks later (prior to randomization), and again at treatment weeks 4, 8, and 12. An appropriate randomization and blinding scheme was used and the study was analyzed by intention to treat. The only major concern is a high initial dropout rate (unclear from which treatment group) requiring 12 additional women to be enrolled, and a somewhat high subsequent dropout rate (24%). In addition, the use of the Kupperman index is questionable because it includes such symptoms as paresthesias and vertigo, which have little physiologic relationship to low serum estrogen. This was not, however, the main outcome measure.

Outcomes measured Patients were asked to record the number of moderate to severe hot flushes and their use of the study medication each day. The severity of symptoms was assessed at each visit using the Kupperman index, a measure of 12 menopausal symptoms, and a remaining supplement count was performed to assess compliance. The average number of hot flushes per day during treatment was calculated and subtracted from the average number of hot flushes per day at baseline.

Results Of the 104 patients enrolled, 40 taking soy and 39 taking casein completed the 12-week study. At baseline, the median number of hot flushes was 11.4 for the soy group and 10.9 for the casein group. The patients were similar in baseline characteristics. Women taking soy had a 26% reduction in mean number of hot flushes compared with baseline by week 3 and a 33% reduction by week 4. After 12 weeks, the mean number of hot flushes was reduced by 1.59 in the soy group after subtracting the effect of placebo; mean change in hot flushes -5.01 (soy group) and -3.42 (placebo group). The Kupperman index values were unchanged. Twenty-five

patients stopped the trial prematurely, 11 in the soy group and 14 in the casein group. Gastrointestinal side effects and food intolerance were the major cause of dropout for 14 patients; constipation was reported in 50% of study subjects.

Recommendations for clinical practice **Soy protein appears to be effective in reducing vasomotor symptoms, but the modest efficacy (hot flushes were reduced, not eliminated) and high incidence of GI intolerance will limit its usefulness in clinical practice. In addition, a soy supplement may not confer the benefits of dietary soy intake. There is a growing body of literature on phytoestrogens and their health effects. A recent review suggests that these naturally occurring compounds reduce cholesterol, improve osteoporosis, and appear to inhibit the growth of different cancer cell lines in culture and in animals.[1] More research is needed to identify which classes of phytoestrogen in food substances (or supplements) are the most effective and whether long term human studies will confirm these benefits.**

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Ruling Out DVT

Cogo, A, Lensing AWA, Koopman MMW, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. BMJ 1998; 316:17-20.

Clinical question **Is it safe to withhold anticoagulation from patients with clinically suspected deep vein thrombosis (DVT) but with normal findings on compression ultrasonography?**

Background Compression ultrasonography is the noninvasive method of choice for evaluating patients with clinically suspected DVT. This test has a high sensitivity and a high specificity for detecting DVT using a simplified technique of compressing single veins in the groin and popliteal fossa. However, it cannot accurately evaluate the calf veins, where thrombosis is relatively common. Because calf vein thrombosis can extend into the popliteal vein, it is currently recommended that all initially normal test results be followed by two repeat tests (one the following day and one a week later) before safely withholding anticoagulation in symptomatic outpatients. This study examines the effectiveness of a modified ultrasound examination that includes imaging of the calf veins and a repeat examination on day 7 for patients with an initially normal test result.

Population studied The study included 1703 adult outpatients with a suspected first episode of DVT who were referred to study centers in Italy, Canada, and the Netherlands. Patients who were taking anticoagulants for more than 48 hours, had symptoms of pulmonary embolism (PE), had a contraindication to contrast venography, or who were unable to be available for follow-up were excluded. The mean age was 63.9 years and the median interval between onset of symptoms and testing was 6 days.

Study design and validity This was a multicenter, prospective cohort study with a 6-month follow-up period. Each subject with an initial normal ultrasound result was retested in 7 days. Each test used the spot vein compressibility technique that images the common femoral vein at the inguinal ligament and the distal popliteal vein to the trifurcation of the calf veins. Doppler-duplex or color-flow studies were not used. Anticoagulation was withheld if both ultrasound results were normal. Confirmatory venography was performed on an unreported number of patients. Rates of false-positive and false-negative ultrasound results were not reported. Patients with abnormal results were given anticoagulation therapy in the usual fashion; patients with normally compressible veins were not treated with anticoagulants. Follow-up rates were not reported but appeared to be very high.

Outcomes measured The primary outcomes were the rate of thromboembolic complications, defined as occurrence of PE before day 7 and the rate of PE or DVT during the 6 months of follow-up.

Results The prevalence of DVT was 24%. Repeat testing (on patients with initially normal test results) accounted for 3% of all DVT diagnoses. The rate of thromboembolic complications was 0.7% (95% CI, 0.3 - 1.2) in the group of patients with initially normal ultrasounds. This rate of complications is at least as low as previously published rates using much more aggressive follow-up testing after normal results. One subject developed PE before day 7 and one developed PE during the 6-month follow-up period; seven subjects developed DVT during follow-up. Imaging of the distal popliteal vein accounted for 6.3% of DVT diagnoses in the first 7 days. The negative predictive value (NPV) is the chance that a patient with a negative test result does not have DVT. We calculated the NPV for the first scan as 98.4%; the second scan increased the NPV to 99.3%.

Recommendations for clinical practice **This study provides a safe, effective method for follow-up of patients with suspected DVT. In a very simi-**

lar study that evaluated 405 patients at a VA hospital, the rate of thromboembolic complications in patients with two normal results 1 week apart was almost identical at 0.6% (95% CI, 0.07 - 2.13).[1] Patients with an initially normal compression ultrasound result should therefore have a repeat examination in 7 days, and they do not require anticoagulation therapy; fewer than 1% of patients managed this way will have a thromboembolic complication.

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Decreasing Complications in Type 2 Diabetes

Gaster B, Hirsh IB. The effects of improved glycemic control on complications in type 2 diabetes. Arch Intern Med 1998; 158:134-40.

Clinical question **Does intensive treatment (tight control) of blood glucose in patients with type 2 diabetes prevent complications?**

Background Type 2 diabetes affects more than 3% of American adults and more than 10% of those older than 65, most of whom are cared for by primary care physicians. These patients suffer many complications attributed to their diabetes, and epidemiological data suggest a direct relationship between the degree of hyperglycemia and the incidence of microvascular complications. The Diabetes Complications and Control Trial (DCCT) showed that tight glycemic control could reduce the risk of the onset and progression of microvascular and neuropathic complications in patients with type 1 diabetes,[1] but no large, long-term trial has been performed on patients with type 2 diabetes. As a result, there is uncertainty as to how aggressively to treat hyperglycemia in these patients.

Study design and validity This was a systematic review of all relevant English language studies published since 1970. Articles were located using a MEDLINE key word search and reference list review. Studies were excluded that did not differentiate between type 1 and type 2 diabetes, did not use adequate measures of glycemic control (glycosylated hemoglobin [HbA_{1C}] or foreign-body-type granulomata), or did not provide analyses of statistical significance.

Outcomes measured The analysis focused on the relationship between glycemic control and the incidence of microvascular, neuropathic, and macrovascular complications, as well as hypoglycemic episodes.

Results The effect of tight glycemic control on microvascular complications has been explored in three controlled trials. Two of these studies used insulin and demonstrated benefit of tight control (HbA_{1C} averaging 7.1% and 7.3%, respectively). The first of these studies, however, was performed in Japan and included 110 patients who may have had absolute insulin deficiency (instead of the insulin resistance more commonly seen patients with type 2 diabetes in the West). The second trial was able to demonstrate a decrease in the progression from microalbuminuria to albuminuria in the tight control group, though the effect of tight control on the development of renal failure is not known. There was no difference in the incidence of retinopathy after 2 years of therapy. The third study, a larger and longer trial done more than 20 years ago, showed no significant differences between the two groups but there were problems with the methodology.

The prevention of macrovascular complications by tight control has been explored in three controlled trials, with none demonstrating a benefit. Three studies showed a substantially lower rate of hypoglycemia than in the DCCT, as long as the average HbA_{1C} was greater than 7%.

This review did not try to combine the results of the various trials as is done when performing meta-analysis. The authors appropriately assessed the validity of the original data, though their conclusions were overstated considering the evidence presented.

Recommendations for clinical practice **Present evidence does not support the recently published recommendation of the American Diabetes Association to maintain HbA_{1C} below 7% in patients with type 2 diabetes.[1] No data exist from large, randomized controlled trials to clearly define the balance between the risks and benefits, as well as the feasibility and cost-effectiveness, of aggressive glycemic control for these patients.**

Studies have suggested that the risk of microvascular complications in type 2 diabetes does not rise dramatically until HbA_{1C} levels are >8%, and hypoglycemia does not appear to be of significant concern with HbA_{1C} >7%. It seems reasonable to aim for the goal of maintaining the HbA_{1C} between 7% and 8% in our patients with type 2 diabetes. The results from a large, long-term British trial studying patient-oriented outcomes that will be pub-

lished this year may help clarify the benefits of tighter glycemic control.

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Lessening the Pain of Lidocaine Injection

Scarfone RJ, Jasani M, Gracely, EJ. Pain of local anesthetics: rate of administration and buffering. Ann Emerg Med 1998; 31:36-40.

Clinical question **Can the pain associated with subcutaneous injection of lidocaine be lessened by buffering the lidocaine or by injecting it more slowly?**

Background Infiltration of intact skin with lidocaine is a common procedure in family practice and acute care clinics. Often, injection of the anesthetic is the most painful part of the procedure for the patient. Thus, there has long been interest in finding ways to decrease the pain of anesthetic injection. Previous studies have assessed specific agents, buffering, temperature, depth of injection, areas of the body anesthetized, needle size, and volume. No previous studies have examined the effect of the rate of administration on the degree of pain experienced.

Population studied Forty-two adult hospital employees participated. Pregnant subjects and those known to have an allergy to local anesthetic agents were excluded.

Study design and validity This was a randomized, prospective, single-blinded study comparing the pain of four methods of lidocaine administration: slow and buffered (SB), slow and unbuffered (SU), rapid and buffered (RB), and rapid and unbuffered (RU). Buffering was accomplished by mixing 1% lidocaine with 8.4% sodium bicarbonate in a ratio of 9 units of lidocaine to 1 unit of bicarbonate. Each injection consisted of 1.0 mL of lidocaine solution (buffered or unbuffered) delivered by a 27-gauge needle at a 45° angle to a depth of 0.25 in. Injections were given in the subject's forearm, in a random rotation of sites (two sites on each arm). Slow injections were delivered over 30 seconds; rapid injections were delivered over 5 seconds. Great care was taken to standardize the method of injection, but there is a potential for bias in that the investigators, who also performed the injections, were not blinded to the rate or buffering status of each injection. Also, the population (adult hospital employees) may not be representative of typical patients, and did not include children.

Outcomes measured Subjects rated the maximal pain of each of the four administrations on a 10-cm visual analogue scale. They were also asked to report which of the injections was the least and which was the most painful, and to compare needle stick pain with infusion pain.

Results Slow administration produced significantly less pain than rapid administration. While there was no significant difference between pain scores for SB and SU, RB produced significantly less pain than RU. Rate of administration produced greater changes in pain scores than did buffering status. Administration rate had a greater impact in the unbuffered than the buffered conditions. SB and SU were significantly more likely to be rated as the least painful injections.

Recommendations for clinical practice **In clinical practice, the value of this pain reduction needs to be weighed against the increased procedure time, especially if multiple injections are required. Further studies should evaluate the effect of infusion rate on exposed dermis (as in a laceration repair) and add lidocaine temperature to the variables. For now, physicians looking to reduce the pain of lidocaine injection should take a few extra seconds injecting the lidocaine rather than taking a similar amount of time to prepare a buffered solution.**

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Rescreening of Pap Smears

O'Leary TJ, Tellado M, Buckner SB, Ali IS, Stevens A, Ollayos CW. PAPNET-assisted rescreening of cervical smears. Cost and accuracy compared with a 100% manual rescreening strategy. JAMA 1998; 279:235-7.

Clinical question **Are computer-assisted devices such as PAPNET useful for rescreening Papanicolaou (Pap) smears?**

Background The Pap smear has contributed to a significant decrease in cervical cancer mortality, but a conventional cytological examination misses a significant number of premalignant cells.[1] The FDA has recently approved several computer devices to

rescreen Pap smears to help avoid missing cervical abnormalities. This study evaluated the effectiveness of the PAPNET rescreening device in identifying cellular abnormalities.

Population studied The population studied included women aged 12 to 89 years from American Air Force communities across the United States and Japan (active duty, retired military personnel, eligible wives and daughters) between 1994 and 1995 who underwent routine Pap screening. In this population, using conventional cytologic screening, 95% of the results were diagnosed as within normal limits (87%), as infection (3%), or as reactive changes (5%). Approximately 2% were diagnosed as low- or high-grade squamous intraepithelial lesions (LGSIL or HGSIL); from 2% to 3% were diagnosed as atypical squamous cells of undetermined significance (ASCUS) or atypical glandular cells of undetermined significance (AGCUS), and the rest were classified as unsatisfactory. Invasive carcinomas are identified only rarely.

Study design A total of 5478 cases were identified as within normal limits or as benign epithelial changes at both primary screening and at a 10% random rescreening. These slides were imaged using the PAPNET system and digitized images of the most abnormal regions were reviewed by one of four individuals (three cytotechnologists and one cytopathologist). Slides appropriate for review were manually rescreened a third time. If the smear was diagnosed as ASCUS or AGCUS or as a higher grade of abnormal, the case was further reviewed by a panel of three cytotechnologists and three cytopathologists until consensus opinion was achieved.

Outcomes measured The primary outcome measured was the proportion of Pap smears initially screened as normal that were later determined to be abnormal by both PAPNET and consensus panel. The secondary outcome measured was the cost per additional abnormal Pap detected.

Results PAPNET-assisted rescreening identified six abnormal smears (five ASCUS and one AGCUS) that had been interpreted as normal on a single manual rescreening (0.11% of the original 5478). No squamous intraepithelial neoplasia was identified. The one patient reclassified as AGCUS went on to have LGSIL on two subsequent Pap smears. The marginal cost of PAPNET over 100% manual rescreening was $33,781 for each case of ASCUS or AGCUS and $101,343 for each expected case of LGSIL identified.

Recommendations for clinical practice **Every now and then an article comes along that serves as a stark reminder of the importance of differentiating DOEs (disease-oriented evidence) from POEMs. It makes intuitive sense that computer-assisted rescreening devices for Pap smears that improve the detection of abnormal smears should consequently lower the incidence of cervical cancer. In this study, the "missed" abnormal smears detected with PAPNET were low-grade lesions of unknown clinical significance.**

The failure to be screened is the greatest obstacle to prevention of cervical cancer in the United States. The use of high-technology rescreening devices will likely raise the cost of obtaining Pap smears, potentially further limiting the number of women able to afford regular screening. Paradoxically, widespread implementation may actually increase the incidence of cervical cancer. Using resources to encourage women to undergo regular screening and ensure that clinicians use appropriate sampling techniques (obtaining diagnostic cells with optimal sample thickness without air-drying artifacts) will likely be more cost-effective than any rescreening strategy.

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Treatment of Premature Ejaculation

Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. J Urology 1998; 159:425-7.

Clinical question **Which oral pharmacotherapy is safest and most efficacious for treating premature ejaculation?**

Background Premature ejaculation (PE) is a common sexual dysfunction, but optimal management is not clear. Behavioral therapy such as the pause-squeeze technique has been considered the reference standard, but is limited by the need for partner cooperation and by poor long-term success. Newer research suggests that serotonergic drugs are effective in treating PE. This study compared fluoxetine, sertaline, and clomipramine.

Population studied Fifty-three Korean heterosexual men were enrolled for the study. Premature ejacula-

tion was defined as intravaginal ejaculation latency time (IVELT) of less than 2 minutes in more than 50% of sexual intercourse episodes. Patients with psychiatric disorders, erectile dysfunction, sexually transmitted diseases, significant medical illnesses, history of alcoholism or substance abuse, or use of drugs affecting sexual function were excluded. The average age of participants was 44 years; all reported having intercourse at least once per week and were married or in a stable relationship. The referral pattern and the details of medical screening were not described. The patients seem similar to those that family physicians identify with premature ejaculation, although cultural differences and lack of clinical detail may limit the strength of inferences.

Study design and validity This randomized, placebo-controlled, crossover study compared the efficacy and safety of fluoxetine (40 mg), sertraline (100 mg), clomipramine (50 mg), and placebo. The tablets were identical and the patients were instructed that they would be taking four different medications of identical actions. Each patient served as his own control; the order of the medications was random. To minimize side effects, a half dose was given for the first week and then the full dose was taken for a total of 3 weeks, with a 1 week washout between each drug.

In general, the study design is strong. The major weaknesses are the 30% dropout rate and the lack of analysis by intention to treat; both biases would lead to overestimating the efficacy of the medications. The effectiveness of the blinding procedures and the impact of physicians not being blinded is unclear.

Outcomes measured The main outcomes were personal and partner sexual satisfaction, side effects, and latency of ejaculation, all measured by a short self-report form. Assessment of sexual satisfaction is critical for clinical relevance, but the validity of patients' recall of latency time and of asking patients about partner satisfaction is limited. An important outcome not measured is the effect on libido.

Results Of the 53 original participants, 37 (70%) completed the entire study. Clomipramine caused the highest sexual satisfaction rate among patients (52.8%, number needed to treat [NNT]= 3), followed by sertraline (41.7%, NNT= 4.5), fluoxetine (25.0%, NNT= 17.9), and placebo (19.4%). Differences among these drugs were statistically significant ($P < .05$). Even assuming that all losses to follow-up were failures, the NNTs were still impressive. Partner satisfaction was slightly higher for clomipramine (38.9%, NNT= 3.6) than sertraline (30.6%, NNT= 5.1), although this result did not reach statistical significance. Each drug, including placebo, caused a significant increase in the mean IVELT. When compared with placebo (2.27 minutes), both sertraline (4.27 minutes) and clomipramine (5.75 minutes) caused a significantly greater increase in the mean IVELT (all, $P < .01$), but fluoxetine (2.30 minutes) did not. The incidence of side effects with clomipramine (63.9%) was significantly higher ($P < .05$) than that of fluoxetine (36.1%), sertraline (33.3%), and placebo (19.4%); the most common side effects were dry mouth with clomipramine and drowsiness with sertraline and fluoxetine.

Recommendations for clinical practice **This study provides moderately strong evidence that clomipramine and sertraline can improve short-term sexual satisfaction for patients with premature ejaculation. Side effects were minor but common, especially for clomipramine. What this study does not address, however, is the efficacy of long-term usage, the utility of "as needed" dosing, and the comparison with or a combination with behavioral therapy. Clomipramine or sertraline are worth trying, but recognition of the disorder and appreciation of its subjectivity remain the keys to the clinical management.**

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Antibiotics for Acute Maxillary Sinusitis in Adults

Stalman W, Van Essen GA, van der Graaf Y, de Melker RA. Maxillary sinusitis in adults: an evaluation of placebo-controlled double-blind trials. Fam Pract 1997; 14:124-9.

Clinical question **Are antibiotics effective in the treatment of acute maxillary sinusitis in adults?**

Background Antibiotics are commonly prescribed for adult patients who present with complaints consistent with acute maxillary sinusitis. Like acute otitis media, acute sinusitis is generally a self-limited disease. In view of the emergence of many antibiotic-resistant bacterial strains, physicians are being urged to use antibiotics judiciously. Is there sufficient evidence from controlled clinical trials to support the routine use of antibiotics in patients with acute sinusitis?

Population studied One hundred forty adult patients were from a general practice, 61 were from an otolaryngology outpatient department, and 50 were from an undefined setting.

Study design and validity This is a Dutch

meta-analysis. The search for controlled trials was extensive, including a MEDLINE search of 1966 through July 1996, the bibliographies of articles retrieved, and the Cochrane Collaboration database. Inclusion criteria were: randomized, double-blinded, placebo-controlled trials of acute sinusitis in subjects older than age 10. Two general practitioners and two epidemiologists independently rated the studies, followed by an attempt to reach consensus. They used a quantitative score based on 35 explicit criteria regarding internal validity (the ability of the study to accurately answer the question) and external validity (the ability to generalize the results to other patients). There was excellent agreement among the raters after consensus discussions, and in general the methods were sound.

Outcomes measured The primary outcomes were the methodological quality of the studies and the difference in outcome between those treated with and without antibiotics.

Results Of 88 identified clinical trials of antibiotic treatment of acute sinusitis, only three met the inclusion criteria.[1-3] In particular, many did not include a placebo. The methodological quality scores of all three were mediocre for internal validity and poor for external validity. Two trials, one using pivampicillin and one using docycycline, found no effect. The third, using cyclacillin, found a benefit for the antibiotic, but the effect size is not given.

Recommendations for clinical practice **The effectiveness of antibiotic treatment of acute sinusitis is unknown. Because of the inadequate methods of these three older studies (all performed more than 20 years ago), one cannot conclude from this meta-analysis that antibiotics have no effect. Three more recent placebo-controlled, double-blind, randomized clinical trials in general practice settings have been published.[4-6] Of these, two showed no effect[4,5] and one showed a significant clinical effect of penicillin and amoxicillin.[6] The single trial showing an effect required a positive CT scan for enrollment; those showing no effect used less stringent enrollment criteria that were more consistent with those used by primary care clinicians in daily practice. These three recent trials suggest that patients with more severe signs and symptoms may benefit from an antibiotic, while those with less severe findings may do as well without one. Another recent Dutch meta-analysis of studies comparing two or more antibiotics in the treatment of acute maxillary sinusitis also supports this approach.[7] Unfortunately, no adequate placebo-controlled trials of newer antibiotics have been published.**

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Yohimbine for Erectile Dysfunction

Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urology 1998; 159:433-6.

Clinical question **Is yohimbine effective and safe as initial monotherapy for erectile dysfunction?**

Background Yohimbine is a presynaptic alpha-2 adrenergic antagonist derived from the bark of the Central African yohimbine tree. It may exert an effect in erectile dysfunction (ED) by increasing penile blood flow. Yohimbine was approved for sale before the FDA required proof of effectiveness, and studies of effectiveness have provided mixed results. Clinical guidelines published by the American Urological Association recommend against the use of yohimbine.[1] This meta-analysis attempts to clarify whether yohimbine is effective and safe as an initial therapeutic option for ED of organic, psychogenic, and mixed etiologies.

Population studied Adult men 18 years and older with secondary erectile dysfunction.

Study design and validity The authors per-

formed a meta-analysis, combining the results of seven randomized, placebo-controlled, double-blind clinical trials including a total of 419 subjects. Studies were identified by searching medical library databases and were selected for inclusion based on systematic review for bias and methodological quality. The studies included in this analysis used various criteria for defining ED (organic, psychogenic, mixed, and unknown), were of differing sizes (from 11 to 100 patients), and used various doses of yohimbine. This meta-analysis selected double-blind, randomized, controlled trials for inclusion in the analysis, which is important because there is a large placebo effect with any treatment of ED. However, some of the studies used a partial crossover design that may bias results in favor of effectiveness of yohimbine as compared with placebo. A limitation in the study of ED in general is the lack of standardized definitions for positive response to therapy. Outcomes used in the various studies included subjective and objective reports, multiple inventory scales, erectility scale, and polysonography. The authors attempted to address the issue of publication bias but did not include any unpublished data.

Outcomes measured Outcomes reported include improvement of erection, interest in sex, and sexual functioning. Additionally, adverse effects were reported.

Results Yohimbine was demonstrated to be superior to placebo when treating ED (OR = 3.85; 95% CI, 2.22 - 6.67). Each trial demonstrated effectiveness of yohimbine as compared with placebo, although the difference in two of the trials was not statistically significant. Lack of significance is likely because of the studied population, mixed cause of ED, and endpoint measures in these studied. Clinically, the use of yohimbine resulted in an overall positive response over placebo and was well tolerated. Adverse effects (10% to 30%) were generally mild and reversible, including anxiety, headache, gastrointestinal disturbances, and urinary frequency. Hypertension was the most significant side effect reported, and may be of concern for patients with a vascular cause of ED. The severity of adverse outcomes was not reported in this study.

Recommendations for clinical practice **Despite the limitations of this meta-analysis, the clinical data are convincing that yohimbine is effective. Previous recommendations have been based on analyses that included noncontrolled trials and focused only on organic causes of ED. Many patients favor medication over mechanical aids or injections. The side effects are mild and reversible. Yohimbine is relatively inexpensive (the generic formulation costs approximately $.50 per day). On the basis of this meta-analysis, yohimbine can be included in our armamentarium for treating ED.**

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