CME

# Evidence-Based Practice

Answering clinical questions with the best sources

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## WHAT'S INSIDE



NEWS ALERT

## New evidence on reducing morbidity among COPD patients

The only interventions known to prolong life for patients with COPD are smoking cessation and oxygen therapy. However, data now suggest that the use of certain chronic medications in patients with stable COPD can reduce flares and, it is hoped, may eventually be shown to prolong life. The results of the recently concluded TORCH trial (Towards a Revolution in COPD Health) contribute to our current understanding. The TORCH trial evaluated the effect of combining inhaled corticosteroids (ICS) with a long-acting beta-agonist (LABA).

### Contradictory results from ICS monotherapy

The use of ICS alone as a chronic agent in COPD has been the focus of 2 recent but contradictory meta-analyses. The first included 8 trials (N=5,085) that randomly assigned patients with stable COPD to ICS therapy or placebo for at least 1 year.[1] Patients with COPD ranging from mild to severe were included, and the mean bronchodilator response was 12%. Compared with patients in the placebo group, patients receiving an ICS had a lower mortality (hazard ratio [HR] 0.75; 95% CI, 0.57–0.99, *P*=.039). Stratifying by individual trials and adjusting for age, sex, lung function, smoking status, and body mass index did not alter the results (HR=0.73; 95% CI, 0.55–0.96). The search method for the meta-analysis was not specified, somewhat limiting the validity of the results.

A more rigorous meta-analysis[2] reached a different conclusion. Using explicit search criteria, authors identified 12 double-blind randomized controlled trials with a total of 5,618 patients that compared ICS with placebo as chronic COPD therapy. The mean ages of participants ranged from 50 to 66 years, and studies ran from 6 months to 3 years. Exclusion criteria for FEV1 reversibility ranged from 10% to 15%. Overall, no significant difference was noted in mortality during a mean follow-up period of 22.3 months (relative risk [RR] 0.81; 95% CI 0.60–1.08; *P*=.27). However, using data

from the 10 trials that included information on exacerbation rates, chronic therapy with ICS did produce a 33% reduction in COPD exacerbations (RR=0.67; 95% CI, 0.59–0.77). This yields an NNT of 12 for patients with moderate to severe COPD to avoid 1 exacerbation over 17 months. ICS therapy provided no benefit for patients with mild COPD.

## ICS and LABA combination therapy

The TORCH trial, one of the largest COPD trials ever conducted, was designed to compare the effects of using the ICS fluticasone in combination with the LABA salmeterol. A total of 6,112 patients (76% male, 43% current smokers) were recruited from nearly 450 sites in 42 countries and followed for 3 years. All had moderate to severe COPD (FEV1/FVC ≤0.7; FEV1 ≤60% predicted; and ≤10% reversibility in predicted FEV1) and a history of at least 10 pack-years of smoking. Patients were randomized to 4 equally sized treatment arms: placebo inhaler, salmeterol 50 µg, fluticasone propionate 500 µg, or salmeterol 50 µg together with fluticasone 500 µg in a single inhaler. All therapies were dosed at 1 inhalation twice a day. The primary outcome measure was all-cause mortality. The study was powered to have a 90% chance of detecting a 4.3% difference in death at 3 years.

Results of the TORCH trial were recently published.[3] Neither salmeterol alone nor fluticasone alone resulted in an improvement in all-cause mortality over placebo (HR=0.88; 95% CI, 0.73–1.06; and HR=1.06; 95% CI, 0.89–1.27, respectively). However, a strong trend toward reduced mortality was seen with combined ICS and LABA compared with placebo (HR=0.83; 95% CI, 0.68–1.00; $P$=.052). The absolute mortality rate in the combined therapy group was 12.6% compared with 15.2% in the placebo group. Only when these results were stratified using Cox's proportional hazard model in a secondary analysis did the difference in mortality between the combined therapy and placebo groups become significant (HR=0.81; 95% CI, 0.67–0.98; $P$=.03).

The mean annual rate of moderate-to-severe exacerbations per participant was 1.13 with placebo, 0.97 with salmeterol, 0.93 with fluticasone, and 0.85 with combined ICS plus LABA. All treatments were significantly better than placebo for reducing exacerbations, and combination therapy was significantly better than either medication alone (12% reduction vs salmeterol alone, $P$=.002; and 9% reduction vs fluticasone alone, $P$=.024).

In terms of adverse events, the TORCH study recorded more episodes of pneumonia in both steroid-containing arms (placebo 39, salmeterol 42, fluticasone 69, and both agents 71), but no difference was noted in total lower respiratory tract infection rates or deaths due to pneumonia. There was a nonsignificant increase in nontraumatic fractures (6.3% with combination therapy vs 5.1% with placebo). Bone mineral density at the hip was followed in a subset of US patients; no significant difference was noted between the groups at 3 years (–3.1% placebo, –1.7% salmeterol, –2.9% fluticasone, –3.2% combination therapy).

A key weakness of the study was the roughly 40% dropout rate in all arms of the study. Also, the use of a placebo arm may have discouraged sicker patients from participating, thus lowering the overall rate of death and reducing the chance of finding a significant change in mortality.

Combining the TORCH trial outcome with data from the earlier meta-analyses on ICS strongly supports the idea that the chronic use of ICS alone for management of stable COPD reduces flares but does not alter all-cause mortality. The TORCH trial further provides good evidence that ICS with LABA is more effective than ICS alone for reducing flares.

## Anticholinergic versus beta-agonist therapy

Unfortunately, it is not entirely clear how to integrate the results of the TORCH trial with a recent meta-analysis demonstrating that a completely different class of medications—the anticholinergics—reduces respiratory mortality and COPD flares, whereas beta-agonists were associated with an increase in both.[4] Unfortunately, this meta-analysis could not differentiate between long- or short-acting agents of either class, did not stratify for the effects of concomitant ICS, and did not provide data on all-cause mortality.

## Summary

So, the best available evidence currently holds that COPD patients should be offered something to

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# Large-scale lung cancer screening trial leaves many unanswered questions

In the United States, approximately 95% of patients diagnosed with lung cancer die from the disease. This low survival rate is significantly correlated with the advanced stage of the disease at the time of diagnosis. The 5-year survival rate of patients with stage I lung cancer is about 70%, but declines to 5% for patients with stage IV disease.[1] Early detection could theoretically improve prognosis. Older studies from the 1970s failed to demonstrate any benefit to patients at high risk for developing lung cancer (smokers) by screening with routine chest x-rays. However, studies conducted over the last decade suggest that low-dose chest computed tomography (CT) may become a viable alternative for lung cancer screening among high-risk populations.

Preliminary evidence supporting a role for CT screening came from a cohort of 1,000 smokers (enrolled between 1993 and 1998) who were aged 60 or older and had at least a 10 pack-year history of cigarette smoking.[2] Every participant in the cohort received a chest x-ray and a low-dose chest CT scan. If a nodule was found on x-ray or CT that did not show a "benign pattern of calcification," the patient was classified as having a noncalcified nodule (NCN). Patients with a NCN underwent high-resolution chest CT scanning. If the NCN was confirmed by high-resolution scan and determined to be larger than 10 mm, it was biopsied. If the NCN was 5 to 10 mm in size, the nodule was either biopsied or followed sequentially with high-resolution CT scanning to monitor for growth. A NCN smaller than 5 mm was followed with high-resolution CT and considered benign if no growth was seen after 2 years.

Following these guidelines in the cohort, researchers performed 28 biopsies on the 233 patients found to have a NCN; 27 had lung cancer and 1 had a benign process. No thoracotomies were performed for benign disease. Whereas all of the lung cancers seen on chest x-ray were also seen on low-dose CT, 20 of the CT-documented lung cancers were not seen on the plain film. Overall, compared with chest x-ray screening, low-dose CT detected NCNs 3 times as often (23% vs 7%), lung cancer 4 times as often (2.7% vs 0.7%) and stage I lung cancers 6 times as frequently (2.3% vs 0.4%). The authors concluded that low-dose CT screening markedly enhanced the detection of lung cancer at earlier stages over chest plain films.

Recently, results were published from a larger, international cohort study in which participants underwent both initial and annual low-dose chest CT scans.[3] A total of 31,567 patients from the United States, Europe, Israel, China, and Japan were recruited. Current or former smokers comprised 83% of the cohort, while people with second-hand smoke exposure (12%) or occupational risk for lung cancer (5%) comprised the rest. The median age was 61 years and the median number of pack-years of smoking was 30 (range 0–141 pack-years).

Low-dose chest CT scans were performed near the time of enrollment and then annually, if the initial scans did not show any findings. Management of suspicious lesions found on the initial screen included biopsy for lesions larger than 15 mm and sequential monitoring (with CT or positron emission tomography [PET] scans) for lesions 5 to 15 mm in size. Lesions smaller than 5 mm were followed with annual screening. During the annual screening phase, any new nodules not seen at baseline were either re-imaged at frequent intervals (if <5 mm) or treated with antibiotics (if >5 mm); biopsy (or PET scanning) was recommended if researchers could not confirm that a lesion was benign. The median duration of follow-up was 40 months (range 1–123 months).

continued

Overall, 13% of the participants (4,186) had a lesion on baseline screening that required further evaluation and another 5% (1,460) had abnormalities during annual follow-up. A total of 484 lung cancers were identified; 410 were found on initial screening and 74 during an annual follow-up. Of individuals with lung cancer, 412 (85%) had stage I disease, and the estimated 10-year survival rate for this subgroup was 88% (95% CI, 84%–91%). For the 302 patients who underwent resection within 1 month of diagnosis, the estimated 10-year survival rate was 92% (95% CI, 88%–95%). Operative mortality for lung cancer resection was low (0.5%).

This very large study does show that screening for lung cancer with low-dose chest CT among high-risk patients can detect lung cancer at a curable stage. But, while low-dose chest CT has an average cost of about $200, the cost-effectiveness of massive screening of smokers is unknown. The emotional and physical burden as well as the likely substantial costs of working up false-positive and equivocal results must still be formally evaluated.[4] Clinicians should still encourage smoking cessation, because preventing lung cancer is currently the safest and most cost-effective strategy available. EBP

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# Help Desk

CONCISE ANSWERS TO PHYSICIANS' CLINICAL QUESTIONS

## What topical agents are useful for preventing or treating pregnancy-related stretch marks?

### Evidence-Based Answer

While 2 proprietary creams have been shown to help prevent pregnancy-related stretch marks, they are not widely available and their mechanism of action is unclear. (SOR **B**, based on a single small clinical trial for each product.) Tretinoin 0.1% cream applied daily for 6 months reduces the size of established stretch marks. (SOR **C**, based on conflicting clinical trials.) It is prudent to avoid tretinoin during pregnancy or breast feeding.

A Cochrane review[1] of topical therapies used throughout pregnancy to prevent stretch marks found 2 studies: one using Trofolastin cream (available in Spain, containing *Centella asiatic*a extract, tocopherol, and collagen-elastin hydrolysates) and one using verum cream (tocopherol, essential fatty acids, panthenol, hyaluronic acid, elastin, and menthol). The Trofolastin study was double-blinded and randomized 80 women at less than 13 weeks' gestation to application of Trofolastin or placebo cream once daily. Treatment with Trofolastin significantly reduced the development of new stretch marks (odds ratio [OR] 0.41; 95% CI, 0.17–0.99). The verum study randomized 50 women at 20 weeks' gestation to receive either verum or placebo creams (frequency of application not stated). Treatment with verum also significantly reduced the development of new stretch marks (OR 0.26; 95% CI, 0.08–0.84).

Several studies have assessed the use of topical tretinoin to treat established stretch marks. The earliest study[2] randomly assigned 11 nonpregnant women with pregnancy-related stretch marks to receive either 0.025% tretinoin cream or placebo. No differences were noted between the 2 groups. A subsequent double-blinded study[3] randomized 22 women with "early" stretch marks to receive topical 0.1% tretinoin or placebo for 6 months. Stretch marks treated with tretinoin decreased in length by 14% and in width by 8%, compared with an increase in length of 10% ($P<.001$) and width of 24% ($P=.008$) for placebo. Finally, an open-label

prospective study had 20 women apply 0.1% tretinoin to their pregnancy-related stretch marks in the abdominal area for 3 months.[4] The length of treated stretch marks decreased by 20%. Side effects—erythema and scaling—were seen in about half the patients. Petroleum jelly applied with the tretinoin reduced these symptoms.

A single study of mature stretch marks (striae alba) treated 10 patients with topical 20% glycolic acid.[5] In addition, half of the treatment area received topical 10% ascorbic acid, 2% zinc sulfate, and 0.5% tyrosine, while the other half was treated with 0.05% tretinoin cream. All therapies were applied once daily for 12 weeks. At the conclusion of the study, both therapies had resulted in improvement in the appearance of the stretch marks.

Overall, surprisingly little quality evidence is available concerning therapies for stretch marks. While tretinoin is readily available, retinoids are known teratogens. Using tretinoin during pregnancy or lactation would not be prudent.

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## Are stretching exercises effective for patients with chronic plantar fasciitis?

### Evidence-Based Answer

Plantar fascia-stretching exercises appear to be more effective than Achilles' tendon stretching exercises. This benefit has now been found to persist for up to 2 years. (SOR **B**, based on a single randomized trial.)

Although plantar fasciitis symptoms resolve for most patients within 10 months, up to 10% have persistent disabling pain.[1] In a randomized clinical trial, researchers investigated the efficacy of plantar fascia–stretching exercises compared with conventional Achilles' tendon–stretching exercises for patients with this condition.[2] A total of 101 participants were recruited who had had chronic heel pain for at least 10 months. To be eligible, they had to complain of maximum pain upon palpation of the origin of the plantar fascia on the medial calcaneal tubercle, consistent with a diagnosis of proximal plantar fasciitis, and to have no response to other nonsurgical interventions, such as nonsteroidal anti-inflammatory medication, orthotic devices, and injections.

They were randomly assigned to either plantar fascia–specific stretching exercises or to an Achilles' tendon–specific stretching program. All participants received soft full-length insoles and a 3-week course of celecoxib. They were to perform the stretching procedure 3 times a day for 8 weeks and told to hold the stretch for 10 seconds each time, repeating the stretch 10 times. The primary outcome was change on the Foot Function Index scale (7 different questions with 0=no pain and 10=worst pain imaginable on a visual analog scale); other outcomes included changes in pain, function, and satisfaction. The outcomes were assessed by investigators who were blind to group assignment.

Eighty-two of the original 101 patients came back for an 8-week follow-up, with a higher attrition rate for individuals assigned to the heel-stretching protocol (28% vs 9.8% in the plantar fascia–stretching group). Persons in the plantar fascia–stretching group fared substantially better at follow-up than individuals in the heel-stretching group for several outcomes, including overall improvement (82.6% vs 55.6%; $P$=.014; NNT=4), heel pain all or much better (52.2% vs 22.2%; $P$=.007; NNT=4), and being totally satisfied with treatment (91.3% vs 60.0%; $P$=.007; NNT=4).

In a subsequent follow-up study of this group of patients, the authors found that the plantar fascia–stretching regimen was associated with persistent improvement for as long as 2 years.[3] At their 8-week follow-up evaluation in the original study, all patients (including the Achilles' heel–stretching group) received instruction in the plantar fascia–specific stretching protocol. Two years later, questionnaires were sent to all participants that assessed the pain subscale of the Foot Function Index and an outcome survey related to pain, function, and satisfaction with treatment. Complete data sets were obtained from 66 of the original 82 participants (81%).

**continued**

Overall, 92% of patients reported near or total satisfaction with treatment, 77% reported no limitation in recreational activities, and 94% reported a decrease in pain. Only 24% reported the need to see a clinician for additional treatment during the 2-year follow-up period.

A complete description of the plantar fascia–stretching protocol can be found at http://www.aafp.org/afp/20040215/tips/12.html.


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## How safe and effective is Zostavax® in reducing the incidence of herpes zoster and postherpetic neuralgia?

### Evidence-Based Answer

Varicella zoster virus (VZV) vaccine, Zostavax®, appears safe and markedly reduces the incidence of herpes zoster and postherpetic neuralgia in patients older than 60. (SOR A, based on a high-quality RCT.) The vaccine has not been studied in younger people or in individuals who have had a previous herpes zoster outbreak.

An early systematic review reported results from 3 trials that measured antibody response to administration of varicella zoster virus (VZV) vaccine among older subjects.[1] These "proof of concept" studies demonstrated augmentation of VZV antibody levels in persons receiving live-attenuated varicella vaccine, but did not measure the incidence of herpes zoster or its complications.

More recently, in a randomized, double-blind, placebo-controlled trial, a single dose of live attenuated Oka/Merck VZV vaccine (dose range of 18,700–60,000 plaque-forming units per dose, median potency 24,600) or placebo was administered to 38,546 adults older than 60 years during a 3-year period.[2] All subjects had a prior history of varicella or had lived in the United States for more than 30 years. Most of the subjects had no health-related limitations (51.3%) or mild health-related limitations (38.6%). Immunocompromised persons were excluded from participation. The primary endpoint measure was the burden of illness due to herpes zoster (calculated as the sum of the herpes-zoster severity-of-illness scores of all members of a group divided by the total number of subjects in the group). A secondary endpoint was the incidence of postherpetic neuralgia.

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## EVIDENCE-BASED PRACTICE

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### Statement of Purpose

Evidence-Based Practice (EBP) addresses the most important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format.

### Newsletter Topics

**Transforming Practice:** Research evidence on diagnostic testing or treatment periodically accumulates to a "tipping point" that warrants a change in practice. Each month the editors select one topic for which a substantial change in clinical practice seems justified. Alternates monthly with News Alert.

**News Alert:** A discussion of current issues that affect family medicine today. Alternates monthly with Transforming Practice.

**Help Desk:** EBP authors search the highest quality sources for best evidence (PrimeEvidence and the TRIPS database) in a concise, clinically useful format. If definitive answers are not available from these sources, the editors turn to high-quality, well-referenced sources. Other resources are used at the editors' discretion.

**Topics in Maternity Care:** To keep readers current with trends and new evidence regarding obstetrics and maternity care

**Behavioral Health Matters/Evidence in Nutrition:** Two features which alternate monthly, and present the most current evidence relating to their respective disciplines.

**Drug Profile:** Pharmaceutical information is promoted directly to consumers as well as physicians, and is readily available on the Internet and in other mass media. In each issue of EBP, the editors objectively review the advantages and disadvantages of a featured medication based on scientific evidence.

**Patient Education:** An evidence-based patient summary of a Clinical Inquiry, provided as a tear-out page to be copied and distributed to your patients.

A total of 957 cases of herpes zoster (315 in persons receiving vaccine and 642 in persons receiving placebo) were recorded, in addition to 107 cases of postherpetic neuralgia (27 in persons receiving vaccine and 80 in persons receiving placebo). Patients receiving the VZV vaccine demonstrated a 51.3% reduction in the incidence of herpes zoster ($P<.001$; number needed to treat [NNT]=58 to prevent 1 case of herpes zoster over 3 years), a 61.1% reduction in the burden-of-disease score ($P<.001$), and a 66.5% decrease in the incidence of postherpetic neuralgia ($P<.001$; NNT=364 to prevent 1 case of postherpetic neuralgia over 3 years) compared with placebo.

More persons in the vaccine group than the placebo group had 1 or more adverse events: injection site erythema (35.8% vs 7.0%), pain or tenderness (34.5% vs 8.5%), swelling (26.2% vs 4.5%), and pruritus (7.1% vs 1.0%). During the 42 days after vaccination, participants in the vaccine group had more serious events (not fully described in the published report) than in the placebo group (1.9% vs 1.3%, respectively; $P=.03$). However, a post hoc subject-by-subject analysis did not reveal clinically significant differences between the 2 groups.

The efficacy of the vaccine in people younger than 60 or who have already had 1 episode of herpes zoster is currently unknown.[3]

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## Are SSRIs effective for treating premature ejaculation?

### Evidence-Based Answer

The evidence is good that both paroxetine (Paxil®) and the newer, short-acting, rapid-onset selective serotonin reuptake inhibitor (SSRI), dapoxetine, provide clinically important improvements for patients with moderate to severe premature ejaculation. (SOR **B**, based on controlled and uncontrolled trials.)

Multiple trials have demonstrated the efficacy of paroxetine for treating men with moderate to severe premature ejaculation. Premature ejaculation is typically defined as latency between intravaginal penetration and ejaculation of less than 2 min. In an early uncontrolled trial, 32 men with premature ejaculation (including 14 who ejaculated prior to penetration) were begun on paroxetine 20 mg each evening for 2 months.[1] At 2 weeks, all patients reported improvement in symptoms and a longer interval before ejaculation. Relapse occurred in 90% of the participants within 3 weeks of discontinuing paroxetine at the end of the study.

In a subsequent report, the results of 2 randomized controlled trials were described.[2] In the first, 26 men with moderate to severe premature ejaculation were randomly assigned to take either 20 mg paroxetine or matched placebo as needed 3 to 4 hours before planned intercourse. The mean pretreatment ejaculatory latency time was 0.3 min. At 4 weeks, the mean ejaculatory latency time was 3.2 min in the paroxetine group and 0.45 min in the placebo group ($P<.001$). In the second trial, 42 men were initially randomly assigned to either 10 mg paroxetine or placebo daily for 3 weeks. Then, for the next 4 weeks, the paroxetine group was to take 20 mg paroxetine as needed prior to planned intercourse, and the placebo group took matched placebo as needed. When measured 3 weeks into each phase of the trial, the mean ejaculatory latency time was 4.3 min for paroxetine daily and 5.8 min for paroxetine as needed, compared with 0.9 min for placebo daily and 0.6 min for placebo as needed ($P<.001$ for both comparisons).

Although still investigational, the short-acting, rapid-onset SSRI dapoxetine also appears to be effective for treating premature ejaculation. In a large, randomized placebo-controlled trial, 2,614 men with moderate to severe premature ejaculation were recruited from 121 sites throughout the United States.[3] To be eligible, participants had to have a mean latency between intravaginal penetration and ejaculation of less than 2 min, and to have experienced significant stress or interpersonal difficulties related to this problem. They were randomly assigned to 30 mg dapoxetine, 60 mg dapoxetine, or matched placebo to be taken 1 to 3 hours prior to planned intercourse for 12 weeks. The primary outcome was time from intravaginal penetration to ejaculation as measured by a stopwatch. At baseline,

the mean latency was between 0.90 and 0.92 min for all 3 groups.

At the end of the study, the mean latency was 1.75 min for the placebo group, 2.78 min for the 30-mg dapoxetine group, and 3.32 min for the 60-mg dapoxetine group ($P<.0001$ for either dose compared with placebo). The most common adverse event associated with dapoxetine use was nausea, occurring in 8.7% and 20.1% of the 30- and 60-mg dapoxetine groups, respectively. The FDA is currently reviewing whether to approve use of this agent for men with premature ejaculation.


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## What is the best surgical approach for women with symptomatic fibroids who choose hysterectomy?

### Evidence-Based Answer

Both vaginal and laparoscopic hysterectomies are associated with significantly faster recovery times than abdominal hysterectomy. Laparoscopic hysterectomy, however, is associated with significantly more urinary tract injuries, and the option of vaginal hysterectomy may be limited by the size of the fibroids. Subtotal hysterectomy has not been shown to provide any long-term advantages over total hysterectomy. (SOR **A**, based on meta-analyses.)

Uterine fibroids are common and largely asymptomatic, but may be responsible for menorrhagia, pelvic pain, infertility, or recurrent pregnancy loss. Many therapies are available, including hysterectomy, fibroid myomectomy, fibroid embolization, ablation of the uterine lining, and medical treatment with gonadotropin-releasing hormone analogues.[1] For the woman who chooses a hysterectomy, abdominal, vaginal, and laparoscopic techniques are all available. An abdominal hysterectomy may be subtotal (leaving the cervix) or total (removing both the uterus and cervix).

A recent meta-analysis[2] evaluated RCTs of women undergoing hysterectomy for benign gynecological disease by different techniques. A total of 27 trials were included that involved 3,643 patients. Sixteen trials compared laparoscopic with abdominal hysterectomy, 4 compared laparoscopic with vaginal hysterectomy, 4 compared all 3 approaches, 2 compared vaginal with abdominal hysterectomy, and 1 compared 2 hybrid approaches (both using a laparoscope during a vaginal hysterectomy).

Return to normal activity was faster after vaginal hysterectomy than abdominal hysterectomy than after abdominal hysterectomy (weighted mean difference [WMD] 12.3 days; 95% CI, 4.8–19.9 days) and also faster after laparoscopic hysterectomy than abdominal hysterectomy (WMD 13.3 days; 95% CI, 9.9–16.8 days). No significant difference was noted between the vaginal and laparoscopic technique in days until return to normal activities (WMD –1.1 days; 95% CI, –4.2 to 2.1 days). Laparoscopic hysterectomy was associated with urinary tract injury more often than abdominal hysterectomy (odds ratio [OR] 2.61; 95% CI, 1.22–5.60; NNH=52). There was a trend toward more urinary tract injuries with vaginal hysterectomy than abdominal hysterectomy, but this difference did not reach statistical significance (OR 3.11; 95% CI 0.31–30.9). Women with abdominal hysterectomies tended to spend 1 or 2 more days in the hospital. An important limitation of this meta-analysis was that many studies excluded women with very large uteruses (typically >280 g or 16 weeks' gestational size).

A Cochrane review[3] analyzed the differences in outcomes between subtotal and total abdominal hysterectomies. Three RCTs with 733 participants were included. Subtotal hysterectomy was associated with less operative bleeding, but no difference was noted in the odds of transfusion. Postoperative febrile illness was less likely with the subtotal technique (OR 0.43; 95% CI, 0.25–0.75; NNT=15). However, patients with subtotal hysterectomies were more likely to have cyclic vaginal bleeding after 1 year (OR 11.3; 95% CI, 4.1–31.2; NNH=12). No differences between the 2 procedures were seen in postoperative sexual functioning, quality of life, or time to return to normal activities. EBP


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# Are psychosocial interventions effective in the treatment of infertility?


## Summary

Psychosocial interventions, including counseling and educational programs, may be beneficial for patients dealing with infertility by alleviating anxiety, depression, and infertility-specific distress. Psychosocial interventions have not shown a consistent effect on subsequent pregnancy rates. (SOR **B**, based on a systematic review of randomized trials with inconsistent results.)


## The Evidence

Infertility, defined as an inability to conceive after a year of regular intercourse without contraception, affects an estimated 12% of couples in the United States of childbearing age.[1] The number of people seeking infertility treatment has increased along with the sophistication of technological options offered by reproductive specialists.[2] The psychosocial impact of infertility can be far reaching. One study found that up to 40% of female infertility patients developed depression and more than 80% developed anxiety, depending on the duration and cause of infertility.[3] The relationship between stress or other psychological factors and infertility has been less clear. Studies have found that distress during in vitro fertilization (IVF) was correlated with reduced pregnancy rates, and that depression interferes with conception.[4,5] This relationship may be indirect in that stress and depression may lead to poor health habits, cause couples to drop out of treatment, or cause couples to reduce the frequency of intercourse.[5]

Can psychosocial interventions improve well-being or increase pregnancy rates? A systematic review[5] found 380 studies on the efficacy of psychosocial interventions for infertility. Only 25 studies met criteria for analysis (as independent evaluations on separate populations). The psychosocial interventions evaluated in the review were counseling (cognitive behavioral, psychodynamic, or infertility-specific), focused educational programs (sex therapy, stress reduction, and autogenic training), and comprehensive educational programs (mind/body programs). The review could not calculate effect sizes because many studies did not provide sufficient statistical detail. Thirty five measures of affect, such as the Beck Depression Inventory, Brief Symptom Inventory, and Hospital Anxiety and Depression Scale, were used in 16 of the trials. A positive effect for psychotherapy was documented in 17 of the 35 measures (48.6%). No measure showed a worsening of affect with intervention. Greater positive effects were observed on measures of anxiety than depression.[5]

Interventions did not show consistent positive effects on interpersonal relationships. Only 11 measures of marital and social factors—relationship satisfaction, conflict resolution, intimacy, and social support—were conducted across 9 studies. A significant effect was seen in 3 of the 11 measures (27.3%). The largest effect of psychosocial interventions was on distress specific to infertility, such as "feeling empty or defective." All analyses of infertility-specific measures showed positive effects. Although some differences were noted in the ways in which women and men benefited from treatment, results indicated that men and women benefited equally from psychosocial interventions.[5]

The review also examined the relationship between psychosocial interventions and pregnancy as the outcome variable. Of the 8 studies that measured this outcome and used a control group, 3 showed a positive effect on pregnancy rate, whereas 5 studies showed no effect.[5]

Web sites that provide psychosocial resources and education for patients include RESOLVE.org (the National Infertility Association) and ASRM.org (the American Society for Reproductive Medicine). EBP


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# Does Paxil CR® pan out?

## The Bottom Line

Since Paxil® (paroxetine) lost its patent in 2003 and became available generically, providers have been encouraged to switch to using Paxil CR® (controlled release). Unfortunately, very little data are available comparing Paxil CR with the generic immediate-release paroxetine (paroxetine IR). Most of the data available for Paxil CR are in comparison with placebo.

**Key Points**

- Paxil CR is being advertised as being better tolerated than paroxetine IR
- Both formulations are equally efficacious when treating anxiety and depression
- Paxil CR is associated with lower rates of nausea initially, but after 2 weeks of therapy, nausea rates were equivalent to those associated with paroxetine IR. Discontinuation rates due to nausea were not different between the drugs
- Paroxetine IR should be considered before Paxil CR due to equivalent efficacy, similar compliance and adverse event rates, and cost considerations

## The Pitch

As the patent for Paxil expired in 2003, a "new and improved" version, called Paxil CR, was released. With the introduction of Paxil CR, samples and vouchers for trial medication were made available to clinics, encouraging the switch from the generic paroxetine IR. The manufacturer stated that new medication's "geometrix design" resulted in fewer side effects and consequently lower discontinuation rates.[1] Direct-to-consumer advertisements encouraged patients already taking Paxil to switch to Paxil CR for "continuous relief throughout the day."[1]

## Context

There are approximately 14.8 million American adults who suffer from major depressive disorder.[2] Many people are successfully treated medically with selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, which are generally better tolerated than older agents such as tricyclic antidepressants. However, many patients discontinue SSRIs due to side effects such as nausea, headache, insomnia, and diarrhea. Poor adherence to antidepressants may lead to relapse and increased health care costs.

## The Data

A study (n=640), funded by the manufacturer, compared the efficacy and tolerability of Paxil CR and paroxetine IR by combining data from 2 separate RCTs of each active agent versus placebo over a 12-week period.[3] Patients in the Paxil CR group were started at 25 mg/d, while those receiving paroxetine IR were started on 20 mg/d. The investigators were allowed to titrate the dose to achieve clinical response, but could not exceed 62.5 mg Paxil CR or 50 mg paroxetine IR.

HAM-D scores equally improved in both treatment groups as compared with placebo. After 12 weeks, response rates were 61.2% for placebo, 72.9% for paroxetine IR, and 73.7% for Paxil CR. During the first week of therapy, nausea occurred in all groups but was lower with Paxil CR than paroxetine IR (14% vs 23%, respectively; $P<.05$). However, no significant difference was noted in nau-

**TABLE 1**

**Most common adverse effects in patients treated with Paxil CR, paroxetine IR, and placebo[3]**

| Adverse event* | Paxil CR® (N=212) | Paroxetine IR (N=217) | Placebo (N=211) |
|---|---|---|---|
| Nausea | 50 (23.6) | 67 (30.9) | 30 (14.2) |
| Abnormal ejaculation† | 21 (26.9) | 16 (23.9) | 1 (1.3) |
| Somnolence | 49 (23.1) | 47 (21.7) | 17 (8.1) |
| Dizziness | 41 (19.3) | 36 (16.6) | 10 (4.7) |
| Diarrhea | 39 (18.4) | 29 (13.4) | 15 (7.1) |
| Infection | 20 (9.4) | 27 (12.4) | 13 (6.2) |
| Constipation | 22 (10.4) | 26 (12.0) | 9 (4.3) |
| Female genital disorders† | 14 (10.4) | 8 (5.3) | 1 (0.8) |
| Sweating | 14 (6.6) | 21 (9.7) | 6 (2.8) |
| Tremor | 15 (7.1) | 15 (6.9) | 5 (2.4) |

Values presented as n (%).
*No significant difference was noted in adverse event rates between active treatment groups; adverse events were more common with active drug than with placebo ($P<.05$).
†Percentage corrected for sex.

sea between the 2 active treatment groups in the second week or at any point thereafter. At the end of the study, no adverse effect was statistically different between the 2 active treatment groups (**Table 1**).

The mean daily doses of paroxetine IR and Paxil CR were 38.2 and 48.2 mg, respectively. To achieve daily doses comparable to those used in the study, one would have to prescribe paroxetine IR 40 mg or Paxil CR 37.5 mg *plus* 12.5 mg, which correlates to costs of approximately $39 and $199 per month, respectively. Dropout rates in the 2 active treatment groups were not significantly different. Dropout rates due to nausea were 3% for Paxil CR, 4% for paroxetine IR, and 0.5% for placebo.

Paxil CR was brought to market in hopes to reduce side effects and thus increasing compliance. Due to cost (**Table 2**), equal efficacy, and similar compliance rates, paroxetine IR should be considered first over Paxil CR. EBP

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**TABLE 2**

**Cost of paroxetine and Paxil**

| Drug and strength | Cost* |
|---|---|
| **Paroxetine HCl** | |
| 10 mg | $30.99 |
| 20 mg | $31.90 |
| 30 mg | $36.99 |
| 40 mg | $38.99 |
| **Paxil CR®** | |
| 12.5 mg | $96.24 |
| 25 mg | $97.64 |
| 37.5 mg | $102.41 |

*Prices are for 30 tablets from www.drugstore.com. Accessed January 26, 2007.

**The practice of evidence-based medicine can be divided into the following components:**

- Identifying a problem or area of uncertainty
- Asking a relevant, focused, clinically important question that is answerable
- Selecting the most likely resources to search
- Searching and appraising the evidence found
- Assessing the clinical importance of the evidence
- Assessing the clinical applicability of the evidence
- Acting on and appropriately applying the evidence
- Assessing the outcomes of your actions
- Authoring—summarizing and storing records for future reference

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help reduce COPD flares; anticholinergics, ICS, and/or LABA all appear effective. More data will be needed before we know if ICS with LABA, anticholinergics, or a combination of all 3 agents will be effective for prolonging life. EBP

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Should patients receive 23-valent pneumococcal vaccination more than once?
*Journal of Family Practice*, September 2006, Vol. 55, No. 9

# Pneumonia Vaccine: Do I Need a Second Dose?

Pneumonia is a serious infection of the lungs that affects millions of people each year. It may be caused by bacteria, a virus, or a fungus. The infection can be mild to severe and is occasionally fatal.

Pneumonia vaccine helps the body block infections caused by certain bacteria (called *Streptococcus pneumoniae*). These bacteria are a common cause of severe pneumonia and can also infect the blood and the fluid around the brain. Vaccination is important because once established, infections can be severe and the bacteria may be resistant to antibiotics.

People with heart or lung problems, diabetes, HIV infection, chronic liver or kidney disease, or certain kinds of cancer, and persons who have had their spleen removed, are at increased risk for pneumonia and its complications. The U.S. Advisory Committee on Immunization Practices (ACIP) recommends that children and adults with these risk factors get the vaccine. Pneumonia vaccine is also recommended for all healthy adults age 65 and older.

It takes 2 to 3 weeks after vaccination to reach maximum immunity. How well you build immunity against pneumonia depends on how old you are and how well your immune system is working. You may receive a pneumonia vaccine anytime, even the same day you receive a flu shot.

Unfortunately, pneumonia vaccination does not prevent all cases of pneumonia. Can you increase your protection with a second dose? At this time, there are no conclusive studies that prove a second vaccine is beneficial. However, we do know that the effectiveness of the vaccine may start to decrease after 9 to 10 years and that a second dose after 5 years in people at highest risk seems to do no harm and may prove worthwhile later on.

Your health professional will use current guidelines from the government to determine if you should receive a second vaccine. People who turn 65 and received the vaccine earlier may choose to have a second dose, too. If you are a vaccine candidate, but cannot remember if you had a pneumonia vaccine, you should go ahead and get one.

Only about 30% of people who need the vaccine are getting even 1 dose. If you are a candidate for the pneumonia vaccine, make sure you get vaccinated and ask your doctor if a second dose is right for you. And don't forget that other important adult vaccine: the yearly flu shot.

**For more information**

Pneumonia (American Lung Association)
http://www.lungusa.org/site/pp.asp?c=dvLUK9O0E&b=35691

Health Topic: Pneumonia (Medline Plus)
www.nlm.nih.gov/medlineplus/pneumonia.html

Infectious Disease Center: Pneumonia (Mayo Foundation for Medical Education and Research)
http://www.mayoclinic.com/health/pneumonia/DS00135

# CONTINUING MEDICAL EDUCATION TEST

CME

## Evidence-Based Practice APRIL 2007

For each question, please mark the single best answer by checking the appropriate box.

**1. Which one of the following statements about hysterectomies is true?**
- ☐ a. Conserving the cervix results in improved sexual function and satisfaction
- ☐ b. Laparoscopic hysterectomy is associated with more urinary tract injuries than the abdominal route
- ☐ c. Vaginal hysterectomy is associated with a longer delay until normal function than the laparoscopic route
- ☐ d. Hysterectomy is the only option for fibroids that are symptomatic

**2. Psychosocial interventions are beneficial for infertile people because they are associated with**
- ☐ a. A decrease in number of IVF cycles
- ☐ b. Improved infertility-specific distress
- ☐ c. Increased pregnancy rates
- ☐ d. Reduced divorce rates

**3. Plantar fascia–specific stretching exercise**
- ☐ a. Is associated with improved outcomes compared with heel stretching
- ☐ b. Is poorly tolerated, resulting in high dropout rates
- ☐ c. Has only short-term benefit
- ☐ d. Reduces the need for subsequent surgical intervention

**4. Which of the following products reduces the size of "early" pregnancy-related stretch marks?**
- ☐ a. Tretinoin (0.1%) cream
- ☐ b. Trofolastin cream
- ☐ c. Glycolic acid (20%) cream
- ☐ d. *Centella asiatica* extract

**5. Varicella zoster virus vaccine has been shown to be safe and effective for preventing herpes zoster in which of the following populations?**
- ☐ a. Children <5 years without a history of chickenpox
- ☐ b. Adults <60 years without a history of chickenpox
- ☐ c. Adults >60 years with a history of chickenpox
- ☐ d. Adults >60 years with a recent outbreak of shingles

**6. Advantages of Paxil CR® over paroxetine IR for treating anxiety and depression include**
- ☐ a. Improved compliance due to decreased nausea
- ☐ b. Greater efficacy for treating anxiety and depression
- ☐ c. Continuous relief of depressive symptoms throughout the day
- ☐ d. None of the above

**7. Which of the following inhaled agents, when used consistently, reduces acute exacerbations of COPD?**
- ☐ a. Long-acting beta-agonists
- ☐ b. Corticosteroids
- ☐ c. Anticholinergics
- ☐ d. All of the above

**8. Which of the following regimens is effective for treating premature ejaculation?**
- ☐ a. Paroxetine 20 mg orally 3 to 4 hours prior to planned sexual activity
- ☐ b. Dapoxetine 30 mg orally 1 to 3 hours prior to planned sexual activity
- ☐ c. Dapoxetine 60 mg orally 1 to 3 hours prior to planned sexual activity
- ☐ d. All of the above

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Answer Key: 1. b; 2. b; 3. a; 4. a; 5. c; 6. d; 7. d; 8. d

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