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## Testosterone Therapy in Men Associated with an Increase in the Risk of Nonfatal MI

### Clinical Question

Does testosterone therapy increase the risk of myocardial infarction (MI) in men?

### Bottom Line

Filling a prescription for testosterone therapy is associated with an increased likelihood of experiencing an MI, especially in older men and those with a history of cardiovascular disease. (Level of Evidence = 2b)

### Synopsis

Men are increasingly taking testosterone supplements, even if they are not hypogonadal. In addition to an absence of evidence regarding effectiveness, previous studies have raised concerns about the safety of this practice. These researchers identified a large cohort of men who had received a first prescription for testosterone therapy (N = 55,593) and compared them with men who had received a prescription for a phosphodiesterase type 5 inhibitor (sildenafil [Viagra] or tadalafil [Cialis]; N = 167,279). All had at least 22 months of continuous follow-up; men with a history of MI before the prescription were excluded from analysis of postprescription outcomes. The database does not have information on lifestyle or actual use, only whether prescriptions were filled. The relative risk (RR) of MI was higher during the period after a prescription for testosterone therapy was given than

before (RR = 1.36; 95% confidence interval [CI], 1.03 to 1.81). This effect was more pronounced in patients older than 65 years (RR = 2.19; 95% CI, 1.27 to 3.77) than in younger men (RR = 1.17; 95% CI, 0.84 to 1.63), for whom the increase was not statistically significant. A similar increase in risk was not seen after prescription of a phosphodiesterase type 5 inhibitor. There was a trend toward increasing risk with older age, including an RR of 3.4 (95% CI, 1.54 to 7.66) for men 75 years and older. Younger men with a history of heart disease also had an increased risk of MI. Biological plausibility is enhanced by the fact that risk returned to normal after prescriptions were not refilled.

**Study design:** Cohort (prospective)

**Funding source:** Government

**Setting:** Population-based

**Reference:** Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9(1):e85805.

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## HPV Screening Every Five Years Equal to Pap Smear Every Three Years

### Clinical Question

Is screening for human papillomavirus (HPV) an effective approach to identifying women at low risk of cervical cancer?

### Bottom Line

A single HPV test provides the same degree of protection over five years as a Papanicolaou (Pap) smear does for three years. We may soon see a recommendation for HPV testing as a stand-alone screen, with cytology reserved for women who have an HPV-positive result. We may also be able to extend the screening interval to at least five years. (Level of Evidence = 1b) ▶

### Synopsis

This analysis comes from the Swedescreen randomized controlled trial, which invited women 32 to 38 years of age from 1997 to 2000 to be screened for HPV while also being screened for cervical cancer using standard cytology. Of the 12,091 women enrolled, 387 (3.2%) developed cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and 230 (1.9%) developed grade 3 or worse (CIN3+) over a median 11 years of follow-up. HPV screening every five years had a sensitivity (across both arms of the study) of 89% to 92% and a specificity of 91% to 94% for CIN3+. These numbers are similar to cytology screening results at three years (sensitivity = 77% to 92%; specificity = 98%). The combination of cytology and HPV screening increased sensitivity slightly at five years (92% to 96%). Women with a positive HPV screening result were not at an increased likelihood of being diagnosed with CIN2+ or CIN3+ compared with cytology screening, making the risk of overdiagnosis low.

**Study design:** Cohort (prospective)

**Funding source:** Foundation

**Setting:** Population-based

**Reference:** Elfström KM, Smelov V, Johansson AL, et al. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial. *BMJ*. 2014;348:g130.

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## Varenicline Plus Bupropion SR No Better Than Varenicline Alone for Tobacco Cessation

### Clinical Question

Is the combination of varenicline (Chantix) and sustained-release bupropion (Zyban) superior to varenicline alone for increasing smoking cessation rates in adult smokers?

### Bottom Line

Combination therapy with varenicline and sustained-release bupropion was associated with a significantly higher prolonged abstinence rate compared with varenicline

monotherapy at 12 weeks and 26 weeks in adult smokers attempting to quit. By 52 weeks, however, the difference was no longer statistically significant. Adverse events, particularly anxiety and depression, were significantly more common in the combination therapy group. Combination therapy was significantly more successful for achieving prolonged abstinence at 12, 26, and 52 weeks among heavy smokers (at least 20 cigarettes daily; number needed to treat = 8.6; 95% confidence interval, 4.6 to 71.6). (Level of Evidence = 1b)

### Synopsis

These investigators identified adults (N = 506), 18 years or older, who reported smoking at least 10 cigarettes per day for at least six months and who were in otherwise good health. Patients randomly received (concealed allocation assignment) varenicline plus bupropion SR (combination therapy), or varenicline plus matching placebo (monotherapy) in standard recommended doses. The study protocol consisted of a telephone screening call, 11 brief clinic visits, and three follow-up telephone calls. Individuals masked to treatment group assignment assessed outcomes on the basis of patient self-reported tobacco cessation in the previous seven days, which was confirmed by an exhaled carbon monoxide level of less than 9 parts per million. Complete follow-up occurred for 62% of patients at 52 weeks. Participants who discontinued the study and for whom no further information on smoking behavior was available were considered to have relapsed at the time of dropout.

Using intention-to-treat analysis, combination therapy was associated with a significantly higher prolonged abstinence rate at 12 weeks and 26 weeks compared with monotherapy, but by 52 weeks the difference was no longer statistically significant. There was no difference in weight gain between the two groups, but adverse events—particularly anxiety and depression—were significantly more common in the combination therapy group. No differences were observed to show any treatment effects according to age or sex, but combination therapy was significantly more successful for achieving prolonged abstinence at 12, 26, and 52 weeks ►

among heavy smokers (at least 20 cigarettes daily). The study was 80% powered to detect a predetermined clinically relevant difference between the two treatment groups.

**Study design:** Randomized controlled trial (double-blinded)

**Funding source:** Industry plus government

**Allocation:** Concealed

**Setting:** Outpatient (any)

**Reference:** Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA*. 2014;311(2):155-163.

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## High-Potency Topical Corticosteroids Effective for Alopecia Areata in Children

### Clinical Question

Are high-potency topical corticosteroids more effective than low-potency corticosteroids for alopecia areata in children?

### Bottom Line

Clobetasol propionate, 0.05%, applied in a thin layer for six weeks on, six weeks off, is a highly effective and safe treatment for alopecia areata in children; hydrocortisone, 1%, is not. (Level of Evidence = 1b)

### Synopsis

There are limited randomized controlled trial data regarding treatment of alopecia areata. In this trial, 41 children (age range = two to 16 years) who had at least 10% scalp involvement were randomized to receive a high-potency topical corticosteroid

(clobetasol propionate, 0.05%) or a low-potency topical corticosteroid (hydrocortisone, 1%). Patients who used other corticosteroids, immunosuppressants, recent topical therapy, or recent light therapy were excluded. Patients, physicians, and outcome assessors were all masked to the treatment assignment. The cream was applied twice daily in a thin layer to the affected area for two cycles of six weeks on, six weeks off. The primary outcome was the surface area of hair loss as measured by a dermatologist masked to treatment assignment. The median baseline area of hair loss decreased from 72 cm to 3 cm in the high-potency group, and increased slightly from 49 cm to 55 cm in the low-potency group. A total of 85% of patients in the high-potency group showed at least a 50% reduction in surface area compared with 33% in the low-potency group ( $P < .001$ ; number needed to treat = 2). In addition, there was a 96.5% reduction in scalp surface area affected by hair loss in the high-potency corticosteroid group compared with only 4.6% in the low-potency corticosteroid group ( $P = .002$ ). The primary adverse effect was skin atrophy in one patient with extensive disease, which resolved during the off cycle. Urinary cortisol levels revealed no evidence of adrenal suppression.

**Study design:** Randomized controlled trial (double-blinded)

**Funding source:** Government

**Allocation:** Concealed

**Setting:** Outpatient (specialty)

**Reference:** Lenane P, Macarthur C, Parkin PC, et al. Clobetasol propionate, 0.05%, vs hydrocortisone, 1%, for alopecia areata in children: a randomized clinical trial. *JAMA Dermatol*. 2014;150(1):47-50.

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