

Testosterone patch: The road not taken

Androgens in OTC and off-label drugs may be less rigorously tested and effective than the testosterone patch for treating hypoactive desire in oophorectomized women.

The way to a rational medical decision can be full of twists and turns, for both physicians considering what to counsel and patients considering their options.

Many oophorectomized women with impaired sexual function desperately want to take an androgen to see if it improves their sex lives. Would the possibility of adverse events alter their choice? The road taken would depend on how a woman and her physician weigh the benefits and risks.

With respect to the testosterone patch, that fork in the road may lie some distance ahead. Last December, the US Food and Drug Administration (FDA) Reproductive Advisory Committee unanimously recommended against immediate approval of Procter & Gamble's Intrinsa for use in oophorectomized women, concluding that additional data, especially long-term safety data, would be necessary.

Only oophorectomized women were included in clinical trials of the testosterone patch; this discussion applies only to them.

A complex question

Sexual desire and activity are particularly complex in humans, and it is unlikely that a single factor or hormone controls them. In women, a model that includes biological, psychological, and sociological factors—a biopsychosocial model—is probably best for understanding sexual function. Within this broader biopsychosocial framework, evidence is mounting that androgens play a modest but potentially clinically important role in regulating sexual function.^{1,2}

For example, in a recent high-quality, large-scale trial, 533 oophorectomized women with hypoactive sexual desire who had been taking estrogen for at least 3 months were randomized to 24 weeks with a patch containing testosterone (300 µg/day) or placebo. Total testosterone concentrations increased from 0.16 to 0.66 ng/mL in the women treated with testosterone, but did not change from the baseline of 0.16 ng/mL in the women given placebo.

Women randomized to testosterone reported significant increases in desire, arousal, orgasm, pleasure, responsiveness, and self-image. Over 4 weeks, they reported 1.5 more episodes of sexual activity than before—a modest but significant gain.¹

Some experts concluded it would be better for these women to seek psychological intervention rather than hormone treatment.³ These experts believe sexual complaints in most women are due to problems with self-respect, self-image, and the quality of the relationship with the sexual partner rather than hormone levels.³

A complex answer

Would women who want to try androgens be deterred by the risks? Many probably would not. Given the difficulty of assigning weight to risks and benefits in a complex medical context, it might be best to provide a balanced description of known and potential risks and the modest benefits of androgens, through physician counseling and a well-crafted package insert. The physician and patient could then collaboratively decide whether to initiate therapy.



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FAST TRACK

It is unlikely that a single factor or hormone controls sexual function

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Androgens and sexual function

Studies of how testosterone and estradiol affect sexual function and activity in nonhuman mammals paved the way to the recent findings on their role in humans.

The role of androgens is especially clear in males. In rats, testosterone is a major regulator of penile erection.⁵ It appears to increase the number of erections by influencing central nervous system activity and by increasing the activity of motor neurons that innervate the ischiocavernosus and bulbospongiosus muscles.⁶ In hypogonadal men, testosterone has been demonstrated to be an important regulator of erections.⁷

In females, estrogen, progestin, and androgen all appear to play a role in regulating sexual activity. For example, in oophorectomized nonhuman primates, estrogen increased and progestin decreased sexual initiation.⁸ In another study, both estrogen and testosterone increased sexual initiation in oophorectomized monkeys.⁹ Oophorectomized and adrenalectomized monkeys are sexually unreceptive; however, implantation of testosterone in the anterior hypothalamus restored sexual receptivity, suggesting a central mechanism for some of the actions of androgens.¹⁰

3 available treatments

The FDA's verdict leaves us with 3 strategies to influence circulating androgen levels in oophorectomized women:

- **Dehydroepiandrosterone (DHEA)** 25- or 50-mg oral supplements available over the counter.
- **Combined esterified estrogen (largely estrone sulfate) plus methyltestosterone** available in doses of esterified estrogen 0.625 mg plus methyltestosterone 1.25 mg (Estratest HS, half-strength), or esterified estrogen 1.25 mg plus methyltestosterone 2.5 mg (Estratest).
- **Topical androgens**, such as Testim 1% gel, at a dose appropriate for women.

These agents have not been as rigorously tested in oophorectomized women as the testosterone patch.

Black box warning for aspirin?

Almost every drug has been linked to adverse events, as well as benefits—and we're continually discovering more for widely used medications. For example, daily low-dose aspirin in women appears

to cause 1 major GI bleed and 1 hemorrhagic stroke per 10,000 woman-years of use. It also protects against 3 or 4 ischemic strokes per 10,000 woman-years of use, but not against myocardial infarction.⁴

Is the net result a benefit, harm, or a wash? Since aspirin causes both GI bleeding and hemorrhagic strokes, should it carry a "black box warning"?

Who will decide?

As medical decisions become more complex, it might be best to make *effective* treatments available. Doctors and patients can assess the data and guidelines and decide together on the best treatment.

If we bar access to effective agents, we run the risk of encouraging use of "untested" OTC drugs and off-label prescribing. These medications may be neither as effective nor as thoroughly evaluated as agents that are being withheld.


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REFERENCES

1. Buster JE, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol.* 2005;105:944-952.
2. Shifren JL, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med.* 2000;343:682-688.
3. Enserink M. Let's talk about sex—and drugs. *Science.* 2005;308:1578-1580.
4. Ridker PM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352:1293-1304.
5. Heaton JPW, Varrin SJ. Effects of castration and exogenous testosterone supplementation in an animal model of penile erection. *J Urol.* 1994;151:797-800.
6. Kurz EM, Sengelaub DR, Arnold AP. Androgens regulate the dendritic length of mammalian motoneurons in adulthood. *Science.* 1986;232:395-398.
7. Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. *J Clin Endocrinol Metab.* 1994;78:711-716.
8. Zehr JL, Maestripietri D, Wallen K. Estradiol increases female sexual initiation independent of male responsiveness in rhesus monkeys. *Horm Behav.* 1998;33:95-103.
9. Johnson DF, Phoenix CH. Hormonal control of female sexual attractiveness, proceptivity, and receptivity in rhesus monkeys. *J Comp Physiol Psychol.* 1976;90:473-483.
10. Everitt BJ, Herbert J. The effects of implanting testosterone propionate into the central nervous system on the sexual behaviour of adrenalectomized female rhesus monkeys. *Brain Res.* 1975;86:109-120.

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