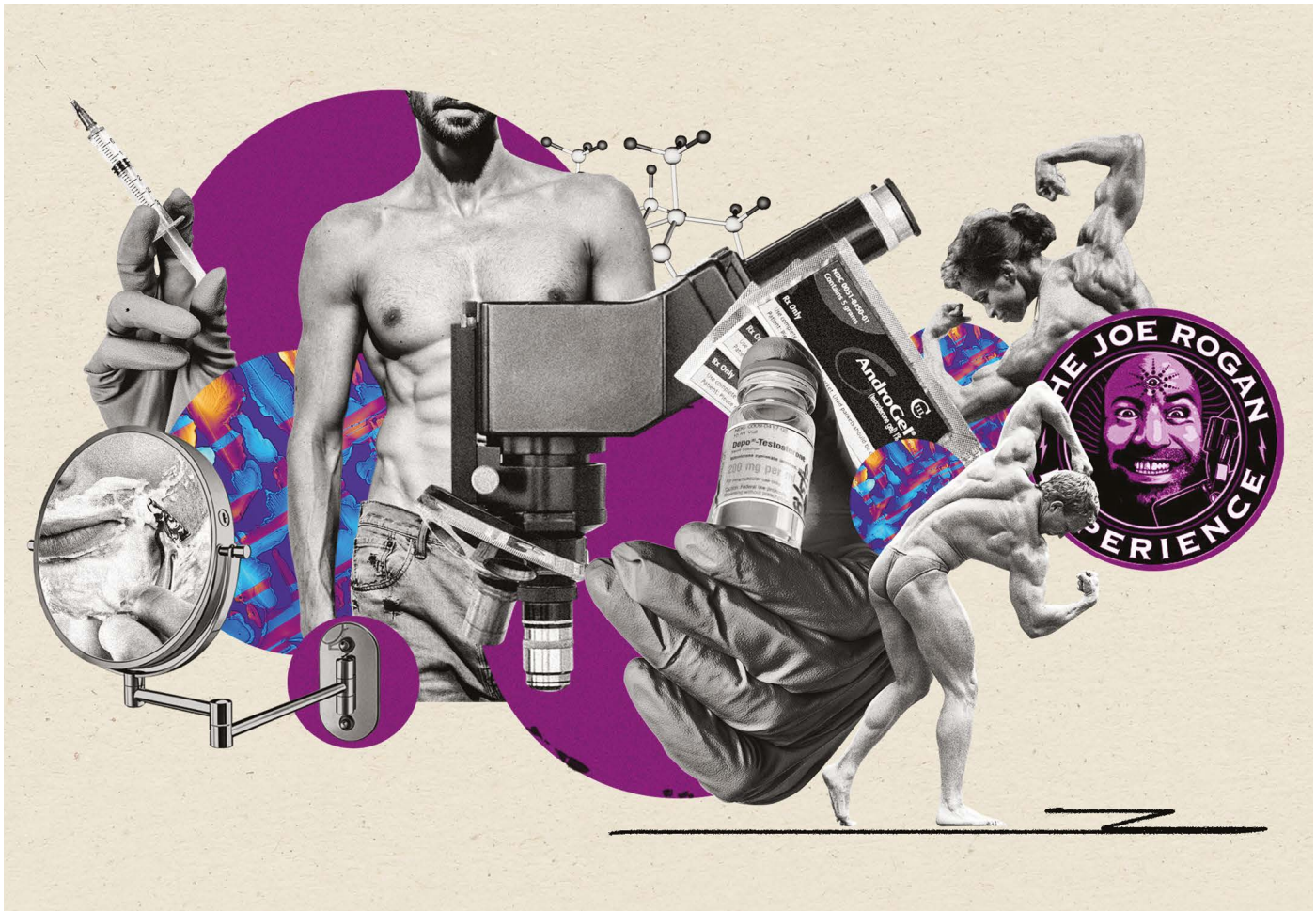

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TESTOSTERONE USE IS TRENDING. WHO REALLY NEEDS IT?

Some clinicians want to broaden the use of testosterone therapy, but there is debate about its benefits and risks. **By Mariana Lenharo**

Is testosterone the next miracle drug? That seemed to be the consensus of an expert panel convened by the US Food and Drug Administration (FDA) in December. It argued for major changes in policy that would expand access to the hormone for people with a range of conditions. Committee members called testosterone replacement "a cornerstone of preventive health" and "a multibillion-dollar preventive-care opportunity".

Testosterone is already available in the United States for people who have low levels of the hormone owing to a known medical issue, such as testicular damage. But evidence is growing that more men — and women — might benefit from the hormone, which is delivered through injections, patches, subcutaneous implants or gels. (This article uses 'men' and 'women' to reflect the language used by the panels and studies cited, while recognizing that trans, non-binary and intersex people are also affected by this issue.)

The panel's recommendations intensify a debate that has been brewing about who might benefit from the treatment. Some clinicians say that most men with low testosterone, especially young ones with no medical issue contributing to the problem, don't need supplemental treatment at all and should be able to raise their testosterone levels by adopting a healthier lifestyle and losing weight. Others argue that men with low testosterone who have symptoms such as low libido, fatigue and irritability could gain from the therapy.

More-enthusiastic proponents, including many members of the FDA panel at the December meeting, take a third view: that all cis men should be tested, and those with low testosterone levels should be treated even if they have no symptoms. "You could make a very strong argument that having a normal testosterone level is important for health and prevention of illness," says Abraham Morgentaler, a urologist at Harvard Medical School in Boston, Massachusetts,

who took part in the December panel.

Morgentaler and other panellists stressed at the meeting that testosterone is not just a 'lifestyle drug' that men take to build muscle and feel good. Yet it is increasingly being marketed that way. Podcasters such as Joe Rogan and his guests have sung the hormone's praises. And scores of testosterone clinics are popping up around the world[1], promising fitter bodies and a boost in energy levels to people who might not even have low testosterone to begin with.

At high doses, testosterone use potentially comes with risks ranging from infertility to increased mortality. The drug is currently classified as a controlled substance with potential for abuse in the United States and several other countries, owing in part to doping scandals in the 1990s and 2000s. That classification is worth reconsidering according to statements made by FDA commissioner Marty Makary, who also voiced his enthusiasm for testosterone at the December panel.

So what is the evidence for the safety and benefits of testosterone replacement?

Safety record

Testosterone's reputation has had its ups and downs since the hormone was first synthesized in the 1930s. After an initial golden period, in which it was described as "one of the most potent drugs recently introduced to medicine"[2], the therapy fell out of favour for fear that it could cause cancer. This idea originated from the work of urologist Charles Huggins who, in 1941, found that prostate cancer depends on testosterone and that lowering the hormone levels caused tumours to shrink[3]. It was a groundbreaking discovery for which he was awarded a share in the Nobel Prize in Physiology or Medicine in 1966.

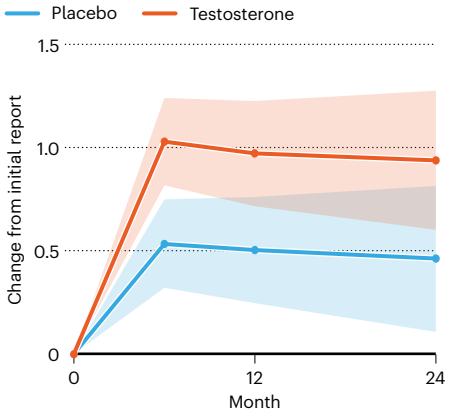
Morgentaler says that when he was training as a urologist in the 1980s, there was a widespread belief, based on Huggins's findings, that testosterone therapy could promote prostate cancer. Despite the presumed risks, he says he still thought that the hormone could help some of his patients who had low testosterone and sexual problems. So, he started treating them while monitoring them closely.

They didn't get cancer, Morgentaler says, and they benefited from the treatment greatly. Some of his clinical findings – along with the revelation that Huggins's most dire warnings about the hormone causing cancer were based on observations of a single person – helped to clear the way for renewed interest in testosterone therapy. Morgentaler is widely recognized for his testosterone-safety work, although some clinicians disagree with him on how much men stand to benefit from the hormone. Morgentaler notes he has consulted for companies that sell testosterone in the past, but says that he has no current financial interests.

Other potential risks cropped up over time. Two retrospective studies from 2013 and 2014 found an increased risk of heart attack in men on testosterone therapy[4,5], which led the FDA to add a warning to testosterone product labels in 2015.

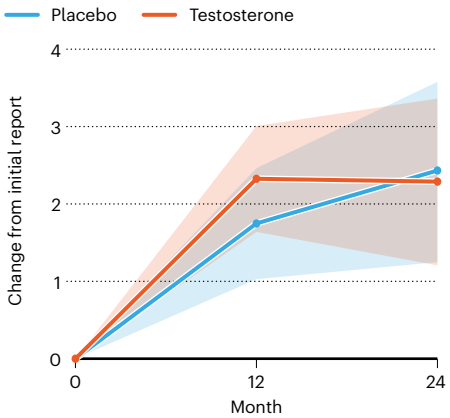
TESTOSTERONE AND SEXUAL ACTIVITY

Men in the TRAVERSE study who received testosterone reported higher levels of sexual activity than did the placebo group at 6 and 12 months.



TESTOSTERONE AND ERECTILE DYSFUNCTION

The TRAVERSE trial found no significant change in erectile function with testosterone replacement compared with placebo.



But a randomized clinical trial involving around 5,200 men – called TRAVERSE – found that middle-aged and older men with low testosterone and a high risk of cardiovascular disease who took the hormone did not have a higher incidence of severe cardiovascular events, including heart attack and stroke, than did those on placebo[6]. "This study only picked very sick people, the greatest-risk population, and nothing bad happened to them," says co-author Mohit Khera, a urologist at the Baylor College of Medicine in Houston, Texas. He also participated in the FDA expert panel and says that he consults for testosterone companies.

On the basis of the TRAVERSE findings, the FDA removed the cardiovascular warning from testosterone products last year.

The safety evidence from TRAVERSE refers to men with confirmed low testosterone levels – below 300 nanograms per decilitre of blood serum – who are treated to bring their levels back to the normal range of 350–750 nanograms. Higher doses, however, that push levels well above the natural range, carry radically different risks.

At high doses, testosterone can thicken the heart's muscles, impairing its ability to pump blood, a condition called cardiomyopathy. High testosterone levels can also cause infertility, shrunken testicles, reduced sperm count and erectile dysfunction, says Channa Jayasena, an endocrinologist at Imperial College London. There are also neuropsychiatric effects, including irritability and even psychosis, which might increase the risk of violent crimes and domestic abuse, says Jayasena, who advises companies that sell testosterone, but says that he declines payment to avoid a conflict of interest. "For reasons we don't fully understand, very high doses of testosterone do something that therapeutic testosterone doesn't do," he says.

A Danish study[7] that followed some 500 men using high doses of anabolic steroids – which include medically approved testosterone products and other variations of the hormone – found that their mortality rate was three times higher than that of non-users over a period of around seven years, a risk that Jayasena says is similar to that of cocaine use. The study participants were caught by a doping control programme that inspects fitness centres in Denmark and tests people suspected of steroid abuse. The authors acknowledge that steroid use has been associated with risk-taking behaviours, which could explain part of the increased mortality.

This form of misuse is also addictive: about 30% of men on high doses become dependent. "They are flooding our clinics," Jayasena adds.

SOURCE: REF. 8

Who can benefit?

Clinicians pushing for broader testosterone use often share striking anecdotes of the hormone transforming people's lives. Morgentaler says that when he started treating people who had low testosterone levels in the late 1980s, they reported back things such as "My wife likes me again", and "I've never had so much patience with my small children". On a regular basis, they tell him that they finally feel like themselves again, with improved mood, vigour and libido. They go from feeling depleted, as if their fuel tank is empty, to regaining stamina and thriving at work, Morgentaler says.

These accounts are from people who stay on the therapy; many drop out. In the TRAVERSE trial, around 61% of participants receiving testosterone discontinued treatment. There is limited research into why men stop testosterone, but Morgentaler guesses that some don't like how it's administered and others just don't feel the benefit (perhaps, he argues, because they are taking the wrong dose or have unrealistic expectations).

Clinical trials support only a modest portion of the benefits that testosterone fans tend to attribute to it.

The clearest effect is in sexual function. A subanalysis of the TRAVERSE trial, which included around 1,100 men with low libido, found that both the treatment and the placebo groups increased their sexual activity, but the increase was 25% greater in treated men[8] (see 'Testosterone and sexual activity'). Sexual desire also improved with testosterone therapy, although erectile function did not (see 'Testosterone and erectile dysfunction').

A meta-analysis commissioned by the Endocrine Society, an organization based in Washington DC, concluded that testosterone was associated with a "small but statistically significant" improvement in sexual function, sexual satisfaction and libido in men with low testosterone[9]. It also found a small improvement in erectile function, contrary to the TRAVERSE trial. The review found no statistically significant difference in energy, mood or cognition.

Other studies have shown that testosterone treatment can effectively treat anaemia and that it improves bone density[10]. Surprisingly, men receiving testosterone in the TRAVERSE trial had more fractures than those on placebo[11]. "It must be that these inactive men were becoming more active", which could be a good thing if that means they are getting more exercise, says Jayasena.

Smaller trials showed that testosterone is also associated with an increase in fat-free body mass and muscle strength, both in younger and older men[12].

Potential benefits for women

As testosterone use surges in some groups, many people who could benefit have mostly been left out of the debate, including trans men, for whom the hormone is recommended as a part of gender-affirming care, and postmenopausal women.

For women, the only indication for which there is clear evidence of benefit is low sexual desire after menopause that causes distress, according to a systematic review and meta-analysis of 36 randomized controlled trials[13].

Susan Davis, an endocrinologist at Monash University in Melbourne, Australia, and a co-author of the review, says that there is huge variation in how women respond to testosterone therapy. Just having a physician listening to their concerns, validating them and caring for them is enough for some women to report feeling better. "I've now studied testosterone in thousands of women and probably done more clinical trials than anybody else with testosterone," says Davis, who consults for companies that sell testosterone and has received grant funding from one. "What we've seen over and over again in all our studies is an incredible placebo effect." Testosterone does do better than placebo in sexual function, but the data do not show a significant difference in well-being, cognitive health and body composition.

Recommended doses – which aim to restore testosterone levels to those of premenopausal women – are generally safe, leading to side effects such as acne, and body and facial hair.

High doses, however, are associated with side effects that some patients might find more unpleasant, such as hair loss, weight gain, voice change and an enlarged clitoris. "It's pretty distressing," says Davis.

She has seen people who have been previously prescribed high doses and report agitation and aggression. Some say they've experienced road rage for the first time. "One woman told me she woke up in the middle of the night with her hands around her husband's neck from a dream," Davis says. Stopping treatment can also be challenging. Some women who suddenly stop after being on high doses "can feel very flat and miserable", she says.

> "LOW TESTOSTERONE IS QUITE A ROBUST BIOMARKER FOR POORER HEALTH OUTCOMES."

Only four countries have testosterone products approved specifically for women: Australia, New Zealand, South Africa and, as of last year, the United Kingdom.

Elsewhere, women are using testosterone formulations designed for men, which might put them at risk, Davis says. This type of off-label use is widespread in the United States. "It would seem to me that the FDA would actually be protecting women by approving a female dose-specific formulation," she says. The FDA panel in December did not discuss testosterone use for women or for trans men.

Regulatory hurdles

The FDA currently limits approval of testosterone products to treat 'classical hypogonadism', in which low testosterone is caused by genetic conditions or disorders of the brain or testicles. In the United Kingdom, Europe and Australia, testosterone is approved for the treatment of men with laboratory-confirmed low testosterone accompanied by symptoms. They do not need to have an identified cause of the deficiency. This is also the position of most clinical guidelines from urology and endocrinology associations around the world.

But the more restrictive regulatory scenario in the United States is already starting to change. In April, the FDA announced it was inviting pharmaceutical companies to submit applications for testosterone therapy for the treatment of low libido in men with low testosterone levels from an unknown cause.

So far, there have been no further changes to US regulations on the basis of proposals discussed by the expert panel, such as removing testosterone's controlled-substance classification or recommending routine testosterone testing for all men. But more changes could still follow.

One argument for including testosterone testing in routine preventive care, said panellist Helen Bernie, a urologist at Indiana University in Carmel, is that low levels have been associated with a range of health risks. For example, Bu Yeap, an endocrinologist at the University of Western Australia in Perth, and his colleagues have reported that older men with low testosterone have a higher risk of stroke[14]. At very low levels, the risk of death from any cause and from cardiovascular disease also increases[15]. Their work also linked low testosterone to a higher risk of dementia and Alzheimer's disease[16].

"We are really aware from the work we've done that low testosterone is quite a robust biomarker for poorer health outcomes, particularly in older men," says Yeap, who has advised and received research support from companies that sell testosterone. But, he adds, the data do not justify testing asymptomatic men. "If you treat all men with low testosterone, will it actually prevent ill health? We haven't proved that."

Answering that question would require a large randomized clinical trial, potentially involving 10,000 older men with low testosterone and increased risk of poor health, followed for at least four years, Yeap says. His team is now working to get funding for such an initiative, which he anticipates will be expensive and complex. "But you've got to get the evidence," he says. "You can't just pre-emptively make assumptions, which is what some people might be doing."

Mariana Lenharo writes for *Nature* from New York City.

1. Grant, B. *et al. J. Clin. Endocrinol. Metab*. https://doi.org/10.1210/clinem/dgaf689 (2026).
2. Aub, J. C. *N. Engl. J. Med*. **222**, 877–881 (1940).
3. Huggins, C. & Hodges, C. V. *Cancer Res*. **1**, 293–297 (1941).
4. Finkle, W. D. *et al. PLoS ONE* **9**, e85805 (2014).
5. Vigen, R. *et al. JAMA* **310**, 1829–1836 (2013).
6. Lincoff, A. M. *et al. N. Engl. J. Med*. **389**, 107–117 (2023).
7. Horwitz, H., Andersen, J. T. & Dalhoff, K. P. *J. Intern. Med*. **285**, 333–340 (2018).
8. Pencina, K. M. *et al., J. Clin. Endocrinol. Metab*. **109**, 569–580 (2024).
9. Bhasin, S. *et al. J. Clin. Endocrinol. Metab*. **103**, 1715–1744 (2018).
10. Snyder, P. J. *et al. Endocr. Rev*. **39**, 369–386 (2018).
11. Snyder, P. J. *et al. N. Engl. J. Med*. **390**, 203–211 (2024).
12. Bhasin, S. *et al. J. Clin. Endocrinol. Metab*. **90**, 678–688 (2005).
13. Islam, R. M. *et al. Lancet Diabet. Endocrinol*. **7**, 754–766 (2019).
14. Yeap, B. B. *et al. J. Clin. Endocrinol. Metab*. **94**, 2353–2359 (2009).
15. Yeap, B. B. *et al. Ann. Intern. Med*. **177**, 768–781 (2024).
16. Marriott, R. J. *et al. Alzheimers Dement*. **18**, 1907–1918 (2022).