

A dangerous elixir?

Testosterone therapy jacks up vigour, sex drive and mental acuity — or so proponents claim. But are those who experiment with this potent sex hormone gambling with their health? Helen Pearson investigates.

It injects a spring into the step, a lift to the libido and a boost to the brain — enthusiasts for testosterone replacement therapy make it sound like a smart, supercharged version of Viagra. No wonder, then, that growing numbers of men — and even a few women — are dosing themselves with the male sex hormone.

In 2003, according to the pharmaceutical consulting company IMS Health, based in Fairfield, Connecticut, the number of American men being prescribed testosterone was over 2 million, having more than doubled from around 900,000 in 1999. The figure is thought to be rising still.

Most of these men are concerned about losing their youthful vigour. But in the medical world, controversy is raging over whether otherwise healthy men, whose testosterone wanes naturally with age, are likely to derive any benefit from such treatments. From what we know about the hormone, testosterone replacement might also accelerate the onset of prostate cancer. All the more worrying, then, that testosterone therapy is likely to be lifelong for some men: almost 30% of those using the hormone are aged between 18 and 45.

The big problem is a dearth of clinical data from which to assess risks and benefits. Indeed, experts say that patients taking testosterone are literally experimenting with their health. “The momentum towards testosterone replacement is reaching a point where it needs serious study to see if it should be supported by the scientific community, or set aside,” says Bill Hazzard, a geriatrician at the University of Washington School of Medicine in Seattle.

On trial

Hazzard was a member of an expert panel convened by the US Institute of Medicine that last year recommended setting up a raft of short-term trials to better establish the effect of testosterone therapy¹. The National Institute on Aging in Bethesda, Maryland, says that it will start organizing such trials in elderly men — who are most likely to benefit from replacement therapy — later this year.

But these trials are unlikely to end the controversy. Some researchers argue that only large, long-term studies will reveal the subtle benefits and risks of testosterone therapy. “I think it’s almost unethical not to do a study like this,” says gerontologist Alvin Matsumoto, also at the University of Washington.

Talk to someone who has taken testosterone, and it’s easy to understand why the



Promise of youth: gels that can be simply rubbed on the skin have boosted testosterone's use.

hormone is in hot demand. Joe Marcklinger, a 58-year-old land surveyor from Boston, turned to testosterone two years ago when he was suffering from depression. After rubbing on daily doses of hormone-laced gel, he not only threw out his antidepressants but had more energy and muscle tone, and a healthy appetite for food and sex. “I felt pretty darn good,” he says. “It turned the clock back ten years.”

In addition to its effects on the brain and behaviour, testosterone fuels the manufacture of men’s sperm, promotes muscle growth and strengthens bones. On the downside, it contributes to male pattern baldness.

Testosterone production by the testes surges upwards around puberty and remains high throughout a man’s twenties and thirties. Its levels then dwindle by about 1% a year². This natural decline has been dubbed the ‘andropause’, because of its parallels with the female menopause. Women also produce testosterone — albeit at less than 10% of the levels found in men — from their ovaries and adrenal glands. Again, production of the hormone seems to decline with age.

The case for testosterone therapy in men

stems from experience with hypogonadism, in which hormone production from the testes is extremely low. Young men with the condition suffer from symptoms associated with ageing — including a loss of muscle, sex drive and mental acuity, plus a gain in flab. Testosterone is an effective treatment.

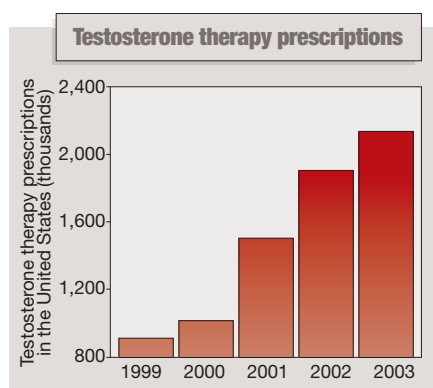
Unreliable evidence

Doctors had wondered for a long time whether ageing men, whose hormones flag to similar levels, might also gain a pick-me-up. But the use of testosterone really took off after the mid-1990s, when injections were replaced with easy-to-use gels and patches. The hormone can also shut down sperm production, which is why it is being investigated as a male contraceptive.

One of the fiercest debates among medical specialists is whether the natural decline in testosterone production has any ill effects. Some experts point to an array of studies linking the decline to failing strength, libido and bone density. But others argue that these naturally deteriorate with age, making it difficult to single out testosterone as a cause. “It might play a role but it’s certainly not the



Some men hope that testosterone therapy will restore their strength and vitality.



only answer," says Lisa Tenover, a geriatrician at Emory University in Atlanta, Georgia.

The second controversy is whether otherwise fit middle-aged and older men benefit from increased testosterone. In one frequently cited trial, led by Peter Snyder at the University of Pennsylvania in Philadelphia, men over 65 who wore a testosterone patch for 36 months gained more muscle and lost more fat than those who donned a placebo³. But in its 2003 report, the Institute of Medicine found that the vast majority of the 31

trials in the literature were small, short and inconclusive.

Then there is the concern that testosterone replacement might increase the likelihood that latent cancerous cells in the prostate gland will transform into tumours. Some cancer therapies slow the growth of prostate tumours by reducing levels of testosterone, but there are few data linking testosterone therapy to an elevated cancer risk⁴. "There's still no convincing evidence," says Darracott Vaughan, a urologist at Cornell University's Weill Medical College in New York, and a member of the Institute of Medicine panel.

The uncertainty is compounded by the unreliability of the techniques commonly used to measure levels of testosterone in the blood. An evaluation earlier this year, led by Christina Wang of the University of California, Los Angeles, found that eight assays that used antibodies to gauge testosterone in the blood often produced over- or under-estimates compared with the gold-standard method of chromatography⁵.

Given these questions, Matsumoto and Glen Cunningham of Baylor College of Medicine in Houston, Texas, teamed up four years ago to propose a large clinical trial to study testosterone's effects. The trial, which grew after revisions into a \$120-million, six-year, project across 40 sites involving 6,000 men, gained support from the National Institute on Aging, the Department of Veterans Affairs and the drug industry.

Cancer fears

But the plan ran into trouble in 2002, when the consortium went looking for financial backing from other institutes at the National Institutes of Health's Bethesda campus. At the time, concerns about hormone therapy in general were running high because of the Women's Health Initiative, a vast study of female hormone replacement that was halted in 2002 after the benefits proved to be outweighed by long-term risks of heart disease, breast cancer and stroke⁶. The halting of that trial led researchers to advise that women on long-term courses of oestrogen and progestin re-evaluate their treatment.

Andrew von Eschenbach, director of the National Cancer Institute, who had previously headed a prostate-cancer research programme, weighed in against the study, citing fears that testosterone could encourage prostate cancer in some of the trial participants. His objection, among other factors, ensured that the trial remained stalled on the starting blocks. "We were disappointed, of course," says Cunningham.

Called in to map a way forward, the Institute of Medicine panel pinpointed the need for more evidence of testosterone's benefits

before embarking on a large-scale trial. Its report recommended a series of smaller investigations looking for gains in strength, sexual function, cognition and quality of life in men aged 65 and over.

But Matsumoto, Cunningham and others claim that the small trials will struggle to show subtle benefits in only a year or two. Far better, they say, to launch a large trial that could — like the Women's Health Initiative — be halted if it revealed serious risks. "They did a major disservice by not suggesting a large trial," argues John Morley of St Louis University School of Medicine, Missouri, a proponent of testosterone therapy. "By the time these studies come out, the baby boomers will have taken testosterone for ten years."

While the debate over male testosterone replacement rumbles on, women are getting in on the act. Most of the attention so far has focused on the hormone's use for treating female sexual dysfunction. One trial, led by Jan Shifren of Massachusetts General

Hospital in Boston, showed that women suffering from low testosterone levels after having their ovaries removed had sex more often after wearing a testosterone patch than those given a placebo⁶. Proctor & Gamble is now seeking regulatory approval to begin market-

ing a testosterone patch designed for use in women in 2005; other pharmaceutical companies are developing similar products.

Once such testosterone formulas hit the market, they raise the prospect that some women will use them as a 'lifestyle' drug — just as Viagra is used by some men who don't have major problems with their potency. Such a prospect worries endocrinologists, who point out that the hormone may prompt acne, the growth of body hair — and perhaps unknown health problems if it is taken for long periods without proper monitoring.

Given this, some experts are calling for larger and longer trials on the safety and efficacy of testosterone therapy in women. "Otherwise, there'll be a big uncontrolled human experiment," says Susan Davis, an endocrinologist at Monash University near Melbourne in Australia. In men, of course, the equivalent experiment is already up and running.

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