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OBSERVATIONS

THE WASHINGTON BRIEF

Increased heart attacks in men using testosterone: the UK importantly lags far behind the US in prescribing testosterone

Drugs containing testosterone are promoted and prescribed differently in the US and the UK, **Sidney M Wolfe** explains

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On 25 February 2014 Public Citizen filed a petition with the US Food and Drug Administration (FDA) to immediately require a black box warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all drugs containing testosterone presently on the market in the United States.[1] In the petition we pointed out that in a large 27 study meta-analysis, the 13 drug industry funded placebo controlled trials collectively failed to show any increase in cardiovascular events in the testosterone subjects, but the 14 non-industry funded trials collectively showed a significant 2.06-fold increased relative risk with testosterone.[2] We have also asked European Medicines Agency director, Guido Rasi, to consider similar action for Europe.[3]

Our petition was also necessitated by a large National Institutes of Health (NIH) funded epidemiologic study published in *PLOS One*, based on records of 55 000 men in the United States who had been prescribed testosterone. This found that the relative risk of heart attacks after using the drug for three months was twice the risk in the year before use in all men aged 65, and it was more than twice the risk in those men under 65 with a history of heart disease. In terms of absolute or attributable risk, the data in the study show that for those 65 and older, the increased risk from use of testosterone is about six heart attacks per 1000 men per year or one per 167 men per year. For those under 65 with a history of heart disease, the increased risk is about 10 per 1000 men per year or one per 100 men per year.[4]

That study involved 45 times more men exposed to testosterone than in the largest previous study. Its size made it possible to examine the risk in younger men but also provided the statistical power to analyze heart attacks rather than overall cardiovascular risk, as earlier studies had done.

Previous studies also included a randomized placebo controlled trial published in 2010 that had to be stopped before completion because of excess cardiovascular events in men randomized to receive testosterone.[5]

Despite this accumulating evidence, the FDA stated that it "has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death."[6] In the face of such accumulating evidence to the contrary, this FDA statement is reckless from a public health perspective. Given the current hype of promotional efforts for drugs for low T (for testosterone), especially in the US, it is not unreasonable to characterize this dangerous newer epidemic, by analogy to the book, hyping estrogen for the menopause, *Feminine Forever*, as a drug industry effort to convince men to stay "Masculine forever," a phrase first used in a 2005 book, *Powerful Medicines*.[7]

The 31 January FDA announcement also made clear that "Testosterone products are FDA-approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure of the testicles to produce testosterone because of reasons such as genetic problems or chemotherapy . . . None of the FDA-approved testosterone products are approved for use in men with low testosterone levels who lack an associated medical condition."

But these advertising campaigns, poorly regulated by the FDA, ensure that many US men who do not meet these FDA specified criteria of both low testosterone levels and an associated medical condition caused by hypogonadism are taking the products nonetheless. Evidence of the success of these campaigns can be seen in the recent finding that almost 25% of men prescribed testosterone in the US had not previously even had a blood test to determine if their testosterone level was low.[8]

A more recent NIH funded study found that, in comparison to the initiation of testosterone use by men in the United Kingdom,

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the population adjusted rate in the US was six times higher in 2000 but rocketed to 17 times higher than in the UK by 2011.[9] The same study found that testosterone testing in previously untreated men was 3.0 times higher in the US than in the UK in 2000 but rose to 3.7 times higher by 2010. A partial explanation for the clear discrepancy between the greater increase from 2000 to 2010 in the comparative rate of new use between the US and the UK and the smaller increase in the comparative rate of new testosterone testing can be found in the study's data concerning reasons for testing and for use. Although in only 0.7% of UK men was fatigue a characteristic listed for testing and 1% a characteristic for use, in the US the comparable figures were 19.8% and 20.4%. Despite the numerical testosterone test results being much more complete in the UK than in the US, the study found that "Those with normal or high levels received testosterone in approximately 1% or less of cases in the UK, while the US treated such individuals in 4% to 9% of cases." Not surprisingly, the authors provided the most plausible explanation for these striking US *vs* UK differences: "Heavy direct-to-consumer marketing of newer testosterone formulations in the US may have led to a much wider interest in testosterone levels and hypogonadism symptoms, resulting in wider testing of men with nonspecific symptoms [such as fatigue] but normal [testosterone] levels rather than targeted testing of symptomatic individuals."

The striking differences in US *v* UK prescribing along with evidence of many men not having testosterone levels checked before being prescribed testosterone drugs as well as the hyped nature of the advertising campaigns guarantee that many men in the US are improperly prescribed testosterone. Despite the previous studies, the current FDA label for these testosterone products is silent on the risk of heart attacks and other cardiovascular diseases, one important, but currently unused antidote to this overprescribing.

Unless the FDA and other countries begin to provide strong, adequate warnings about the risks of heart attacks and other cardiovascular diseases, the continuing toll of heart attacks in people who are not even candidates for testosterone will remain a testament to this other form of steroid misuse, in addition to the better known one in athletes.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and declare that I have no relevant conflict of interest to declare.

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