Androgens: Clinical Research and Therapeutics
Volume 2.1, 2021
DOI: 10.1089/andro.2021.0006
Accepted April 25, 2021

Androgens
Clinical Research and Therapeutics
Mary Ann Liebert, Inc. publishers

EDITORIAL Open Access

Understanding the Controversy Regarding Treatment of Age-Related Testosterone Deficiency

Abraham Morgentaler*

In this volume of *Androgens: Clinical Research and Therapeutics* (the *Journal*), we present the *Journal*'s first point-counterpoint on one of the key issues in the field, namely whether testosterone (T) therapy (TTh) should be offered to men with what has been called "age-related hypogonadism."[1,†] Writing in favor of treatment for men with age-related testosterone deficiency (TD) is Abdulmaged Traish, MBA, PhD, Editor-in-Chief of the *Journal*,[2] and arguing against treatment of these men are Christine Nguyen, MD, and colleagues from the Food and Drug Administration (FDA) in the United States.[3]

The *Journal* is delighted to have such prominent authors express their views, and, in particular, we appreciate Dr. Nguyen and colleagues from the FDA engaging in this timely and much needed scientific debate to explain their position to the public. Indeed, this debate largely exists because of the FDA, which appears to have coined the phrase "age-related hypogonadism" in a 2015 publication in which several of the same authors argued that TTh use should be restricted to men with specific long-known causes of TD and should not be offered to men without those specific conditions. Nguyen and colleagues suggested that low T levels occurred in men without these known conditions "for no discernable reason other than older age."[1]

The controversy arises because professional society guidelines from prominent medical groups such as the Endocrine Society[4] and the American Urological Association,[5] as well as clinical recommendations from other groups,[6,7] make no such distinction based on etiology of TD, and recommend treatment for those with characteristic symptoms and/or signs of TD confirmed by low serum T levels.

As Dr. Traish ably explains,[2] the biological effects and symptoms of TD occur from reduced levels of T, regardless of underlying etiology. So, it has been perplexing to clinicians and researchers alike why the FDA would take the position that a man with a pituitary tumor and a low serum T level would merit treatment, but a man without a pituitary tumor would not merit treatment, even with identical symptoms and serum T levels.

The responsibilities and history of the FDA shed some light on this question. The Food, Drug, and Cosmetic Act signed by President Franklin Delano Roosevelt on June 25, 1938, brought drugs, medical devices, and cosmetics under the FDA's control, requiring approval for all new drugs and labels for their safe use. It is a federal consumer protection agency that was created after highly publicized episodes of deaths and injuries from previously unregulated products marketed to the public. As stated on the FDA's website, its mission statement begins with, "The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices…" (emphasis added).[8] The fact that the word "safety" precedes "efficacy" is consistent with the primary goal of protecting public health. In contrast, health care providers are focused on the care of the individual patient, and the calculus of benefits versus potential harms may differ based on this approach.

†Terminology note: The *Journal* prefers and encourages use of the term "testosterone deficiency" over the older and less specific term, "hypogonadism."

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

*Address correspondence to: Abraham Morgentaler, MD, Beth Israel Deaconess Medical Center, Harvard Medical School, 200 Boylston Street, #309, Chestnut Hill, MA 02467, USA, Email: amorgent@bidmc.harvard.edu

The history of the FDA's relationship with TTh may also play a role. T products have been available since the mid-1930s, but it has only been in the past 20 years that T products were prescribed to symptomatic but otherwise reasonably healthy men with low T levels,[9] what the FDA now refers to as men with age-related hypogonadism. Although this change in prescribing reflects the relatively recent recognition that men without structural anatomical abnormalities, genetic abnormalities, or toxin exposure may still suffer from TD and benefit from TTh, it would be understandable if the dramatic increase in rates of prescribing of a medication under the purview of the FDA would cause a degree of consternation in that regulatory body.

Another key to understanding the mystery of the FDA's position appears to be its interpretation of study results regarding the benefits of TTh. Whereas publication of results of the T trials[10,11] has been widely hailed as confirming previous research showing TTh has a remarkably wide range of benefits in multiple domains, including sexual desire, sexual activity, mood, physical activity, bone mineral density, and anemia, Nguyen and colleagues appear to minimize the importance of those results. They write, "For most of these measures, the publications reported no improvements with testosterone therapies, and for others, the results were of uncertain clinical benefit."[3] Although it is difficult to square the actual results of these sets of studies with the descriptions by Nguyen and colleagues,[3] their apparent belief that TTh provides negligible benefits appears central to their conclusion that TTh use is not merited in the vast majority of men with TD, namely, men with age-related TD.

For the FDA, the safety of any medication is paramount, as it should be. In this regard, Nguyen and colleagues describe the new finding of small elevations in mean blood pressures noted with ambulatory monitoring for two TTh products during drug submission studies and were recently approved with a black box warning regarding risk of hypertension.[3] Although this result was a surprise to the scientific community, it must also be noted that in the recently published T4DM study in which 1007 men with abnormal glucose tolerance tests were randomized to 2 years of either T undecanoate injections or placebo, the differences in mean systolic and diastolic pressures did not differ between the T and placebo groups.[12] Longitudinal registry studies have shown a *decrease* in blood pressure values over time.[13] To explain these disparate findings, one must wonder whether there may be a mild transient adverse effect of TTh on blood pressure, perhaps due to fluid retention, which resolves with prolonged use.

One of the curiosities of modern medicine is that no one is in charge of scientific "truth." There is no universally respected wise guru of medicine, like a medical Yoda from the Star Wars movie series, to provide either the big picture of what the thrust of data show, nor guidance on the details. Instead, we rely on fragmented often contradictory views from what we consider trusted sources: what we learned in medical school from teachers or textbooks, professional medical organizations, and the latest articles published in leading journals. The degree of contradictory information in medical opinion may lead the average clinician to throw up his or her hands and say, "I don't know what to believe." In this state of chaos, the FDA has often been regarded as an arbiter of medical science, and the position of the FDA with regard to TTh, as described by Nguyen and colleagues,[3] has an outsized impact. For this reason, it is imperative for those involved in clinical work or research involving TTh in men with TD to be familiar with the arguments by Nguyen and colleagues[3] as presented in this volume of the *Journal*, as well as the strengths and weaknesses of those arguments.

The FDA is a critically important government institution charged with the protection of our public health. Yet it must be emphasized that its role is to regulate the pharmaceutical industry, and not health care providers. It bears emphasis that *the FDA is not involved with the practice of medicine*. Yet the medical community and insurance companies pay close attention to the FDA's positions, and insurance companies frequently restrict coverage based on FDA labels, especially if it helps their bottom line.

Although pressures on a regulatory agency such as the FDA differ substantially from those of health care providers and medical groups, it is to be hoped that the entirety of the scientific community, including the FDA, will soon come to recognize the importance of TTh not only for its symptomatic benefits in men with age-related TD, but also for its impact on general health. I encourage everyone interested in TD and its treatment to read the excellent articles by Traish[2] and by Nguyen and colleagues.[3]

References

1. Nguyen CP, Hirsch MS, Moeny D, Kaul S, Mohamoud M, Joffe HV. Testosterone and "age-related hypogonadism"—FDA concerns. N Engl J Med. 2015;373:689–691.
2. Traish AM. "Age-related" testosterone deficiency should not be treated: CON. Androg Clin Res Ther. 2021;2(1):46–55.

3. Nguyen C, Hirsch M, Kaul S, Woods C, Joffe H. Testosterone therapy for the treatment of age-related hypogonadism: Risks with uncertain benefits. Androg Clin Res Ther. 2021;2(1):56–60.
4. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715–1744.
5. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. J Urol. 2018;200(2):423–432.
6. Morgentaler A, Traish A, Hackett G, Jones TH, Ramasamy R. Diagnosis and treatment of testosterone deficiency: Updated recommendations from the Lisbon 2018 International Consultation for Sexual Medicine. Sex Med Rev. 2019;7(4):636–649.
7. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008;159(5):507–514.
8. FDA. What We Do. https://www.fda.gov/about-fda/what-we-do, accessed March 30, 2021.
9. Morgentaler A, Traish A. The history of testosterone and the evolution of its therapeutic potential. Sex Med Rev. 2020;8(2):286–296.
10. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374(7):611–624.
11. Snyder PJ, Bhasin S, Cunningham GR, et al. Lessons from the testosterone trials. Endocr Rev. 2018;39(3):369–386.
12. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): A randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol. 2021;9(1):32–45.
13. Traish AM, Haider A, Haider KS, Doros G, Saad F. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: A real-life observational registry study setting comparing treated and untreated (control) groups. J Cardiovasc Pharmacol Ther. 2017;22(5):414–433.

Cite this article as: Morgentaler A (2021) Understanding the controversy regarding treatment of age-related testosterone deficiency, *Androgens: Clinical Research and Therapeutics* 2.1, 61–63, DOI: 10.1089/andro.2021.0006.

Abbreviations Used

FDA = Food and Drug Administration
T = testosterone
TD = testosterone deficiency
TTh = testosterone therapy