THE JOURNAL OF
SEXUAL MEDICINE

INVITED COMMENTARY

# Testosterone Therapy: Do American and European Clinicians Have Different Approaches?

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## INTRODUCTION

Despite its discovery nearly 100 years ago, testosterone remains a controversial and often poorly understood topic. Given the wide discrepancies in opinions on testosterone, the current commentary provides a contrasting discussion on opinions and practice patterns of Europe and the United States. Although it is clearly impossible to accurately and thoroughly categorize entire regions, the current commentaries will attempt to highlight key social and political differences that ultimately serve to mold public opinions, practice patterns, and research biases. See Table 1 for a summary of similarities and differences between testosterone prescribing practices and attitudes in Europe and the U.S.

## CURRENT STATE OF TESTOSTERONE PRESCRIBING

### European Perspective

As soon as testosterone was discovered and synthesized in Germany in the 1930s, it was put to use for various causes. These approaches were rather experimental and went beyond substitution in clinically diagnosed hypogonadism (testosterone assays were not routinely and accurately available). Initially, testosterone was used for wide-ranging indications including enhancing military performance, as well as ameliorating specific symptoms such as angina pectoris. In subsequent decades, testosterone was used primarily by endocrinologists as a replacement and substitution therapy; however, its use expanded in the 1970s when it was increasingly applied to clinical research as a male contraceptive, secondary to its spermatogenic suppressive properties.

The 1990s saw the emergence of new testosterone preparations, such as transdermal patches and gels and long-acting injections, which led to increasing popularity within urology and other specialties. Simultaneously, doubts about the safety of testosterone replacement emerged, especially regarding prostate and cardiac health.[1] This resulted in the institution of many clinical trials, most of which were inadequately powered to provide definitive answers.

At the same time, various societies began developing guidelines for the use of testosterone, which became the backbone for reimbursement of testosterone replacement therapy by health insurance companies. With increasing attention to guidelines and requirements for reimbursement, testosterone administration became more tightly regulated, and specific laboratory and symptomatic factors were mandated along with routine monitoring of treatment parameters (hormone levels, symptomatic outcomes, monitoring for safety).

Beyond traditional indications for testosterone therapy, an unregulated field of "anti-aging" medicine exists in which testosterone is prescribed to patients without proper diagnosis or frequent assessment of sex steroid levels and safety parameters. Patients are then responsible for covering the costs for testosterone preparations themselves. Such events, which are not rare, contribute to increasing concerns about the use of testosterone in general, as well as within the European states.

### U.S. Perspective

Testosterone prescribing patterns and opinions have gone through significant shifts in the United States in the past 2 decades. Beginning in the 2000s, the evaluation of testosterone "deficiency" and supplementation gained traction and resulted in a dramatic increase in testosterone prescriptions and expansion of the testosterone industry. This contrasts to the relatively minor changes in patterns noted in Europe (~90% increase vs >300% increase in the United States).[2,3] During the following decade, however, testosterone prescribing underwent somewhat of a "market correction," as contrary views on the benefits of testosterone became more publicized including statements from the U.S. Food and Drug Administration (FDA).[4,5]

With this history as a backdrop, the current U.S. prescribing landscape is very fragmented. On one extreme, some providers will supplement testosterone without prior testing, without therapeutic monitoring, and with very little oversight. At the other end of the spectrum, some providers will perform extensive laboratory testing, refer patients to other specialists, and strictly limit the dosing and prescribing of testosterone. In this medical atmosphere, patients often "shop" for the type of physician who best meets their desires and needs for supplementation. Of those visiting their long-time trusted physicians, the likelihood of receiving a prescription often depends on the specialty and training of the provider and which particular biases (for or against testosterone) the provider holds at that time.

Despite an abundance of literature on the topic, the general understanding among practitioners on the role, risks, and

Received May 26, 2018. Accepted July 17, 2018.

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https://doi.org/10.1016/j.jsxm.2018.07.010

**Table 1.** Comparisons of testosterone prescribing practices and attitudes between the United States and Europe

| | Europe | United States |
|---|---|---|
| General opinions | | |
| Opinions on testosterone | Divided opinions with pro-testosterone clinicians and backlash against testosterone clinics that provide supplementation without appropriate diagnosis and oversight | Similar to Europe |
| Opinions on treating men with "classical" hypogonadism* | Nearly universally supported | Nearly universally supported |
| Opinions on treating men with age-associated declines in testosterone/ "functional" hypogonadism (eg, testosterone deficiency secondary to obesity) | Support for age-associated and combined therapy with testosterone and comorbid condition management for functional hypogonadism | Dichotomous opinions: guidelines support, FDA suggests off-label |
| Guidelines and policies | | |
| Region-specific guidelines | European Association of Urology, Male Hypogonadism (2012; updated 2018)[6] and Investigation, Treatment and Monitoring of Late-onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA and ASA Recommendations[7] | American Urological Association, Evaluation and Management of Testosterone Deficiency: AUA Guideline[10] |
| Government restrictions on physician payments | Strict regulation of industry payment to physicians, including easily searchable monetary payments to physicians | Strict regulation of industry payment to physicians, including easily searchable monetary payments to physicians |
| Manufacturing regulations | European Medicines Agency and country-specific agencies regulate sale/distribution of commercial products; pharmacies selling testosterone products are regulated by national or regional institutions and are only allowed to sell the product when it is prescribed | FDA regulates sale/distribution of commercial products; state pharmacies regulate compounded preparations |
| Insurance coverage | | |
| Coverage for testosterone | Varies by country, individual, and therapy; patient costs may range from minimal to up to the equivalent of $200/mo for prescriptions | Varies significantly by region, individual, and therapy; patient costs may range from minimal to $300–$400/mo for prescriptions |
| Coverage for clinical visits | Covered by nearly all insurance plans | Covered by nearly all insurance plans |
| Market | | |
| Market for testosterone | Includes traditional indications (low testosterone + symptoms) and the "anti-aging" market | Similar to Europe |
| Advertising | Any form of advertising pharmaceutical products that require prescription is prohibited, including testosterone preparations | Direct-to-consumer advertising permitted |
| Rate of prescriptions | UK: 90% increase from 2001 to 2010[2] | 359% increase from 2001 to 2011†,[3] |

FDA = U.S. Food and Drug Administration.
*Classical hypogonadism defined herein as unequivocally low testosterone in the setting of hypogonadotropic hypogonadism or hypergonadotropic hypogonadism, particularly in younger men; excludes men with borderline low testosterone or those with age-associated testosterone declines.
†Indicates rate of testosterone use among men ≥40 years.

benefits of testosterone therapy is often quite limited. Similarly, the routine use of standardized testing, including regular testosterone levels, occurs in only a minority of cases, in spite of consistent recommendations indicating such a need.[3] As such, although a general consensus on various aspects of testosterone exists among multiple specialties, the translation of these best practices to clinical practice is lacking.

## MOTIVATIONS

### European Perspective

As research on testosterone yielded results, which were seen as having potential benefits beyond the field of sexual medicine, namely regarding metabolic and bone health, more physicians became interested in prescribing this hormone. This knowledge,