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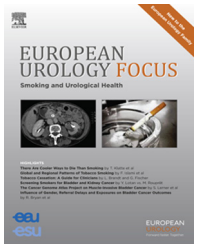

Review – Aging Male

Marketing and Testosterone Treatment in the USA: A Systematic Review

Jathin Bandari [a,*], *Omar M. Ayyash* [a], *Sherry L. Emery* [b], *Charles B. Wessel* [c], *Benjamin J. Davies* [a]

[a] *Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;* [b] *NORC, University of Chicago, Chicago, IL, USA;* [c] *University of Pittsburgh Health Sciences Library System, Pittsburgh, PA, USA*

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Abstract

Context: Testosterone replacement therapy (TRT) is currently approved by the Food and Drug Administration only for classic hypogonadism, although off-label indications have resulted in a dramatic expansion in prescriptions in the USA. Marketing may significantly affect prescriber behavior.
Objective: To systematically review all available evidence on marketing and TRT in the USA.
Evidence acquisition: PubMed, Embase, and Scopus were searched up to July 2017 for all relevant publications reporting on assessments of the TRT market size, economic costs associated with hypogonadism, trends in TRT prescriptions, drug discontinuation rates, and advertising and sales efforts in the USA.
Evidence synthesis: Twenty retrospective studies were included in the final analysis. The market size for hypogonadism constitutes 5.6–76.8% of men in the USA, with the lower end of the range representing the strictest criteria for diagnosis. Men with a diagnosis of hypogonadism consume $14 118 in direct and indirect costs to the payer. Over the last 2 decades, TRT prescriptions have increased between 1.8- and 4-fold. After 1 yr, 80–85% of men discontinue TRT. There is an association between direct-to-consumer advertising and testosterone testing, TRT prescriptions, and TRT without testosterone testing. There is a high prevalence of misinformation on Internet advertising.
Conclusions: Off-label indications have driven the dramatic expansion of TRT prescriptions over the last 2 decades. Direct-to-consumer advertising poses a unique challenge in the USA. Overtreatment can be avoided by applying strict diagnostic criteria for hypogonadism, which limits the addressable market for TRT.
Patient summary: In this report, we reviewed the relationship between marketing and testosterone therapy in the USA. We found that many patients are prescribed testosterone without an appropriate diagnosis of hypogonadism, which may be related to the marketing efforts for off-label prescribing.

* Corresponding author. University of Pittsburgh, 3471 Fifth Avenue, Suite 700, Pittsburgh, PA 15213, USA. Tel.: +1 412 692 7932; Fax: +1 412 692 4101.
E-mail address: bandarij@upmc.edu (J. Bandari).

1. Introduction

Despite its first clinical application in 1937, testosterone is currently approved by the Food and Drug Administration (FDA) only for classic hypogonadism—primary or secondary hypogonadism caused by specific conditions related to the disruption of the hypothalamic–pituitary–adrenal axis or gonadal toxicity [1]. Based on its historical use, clinical trials are only required to demonstrate return to normal serum testosterone levels rather than resolution of clinical hypogonadism. Despite the rarity of these entities, off-label use of testosterone replacement therapy (TRT) has resulted in a

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dramatic expansion in prescriptions in the USA over the last 2 decades [2]. This has raised concerns over whether or not pharmaceutical marketing efforts, rather than well-performed clinical trials, is a driving force for TRT adoption [3].

The application of TRT to offset the effects of "age-related hypogonadism" or "andropause" is difficult to ascertain due to considerable heterogeneity in the definition of hypogonadism. Investigators have adopted two forms of definitions: statistical and clinical. The statistical approach utilizes serum testosterone measurement and chooses percentile cutoff values (eg, 25th percentile), which possesses the advantage of objective measurements at the expense of clinical applicability [4,5]. Conversely, the clinical approach more closely resembles actual practice patterns, but its constellation of highly subjective signs and symptoms has resulted in poor sensitivity and specificity in validated questionnaires [6,7]. According to the Clinical Affairs Committee of The Endocrine Society [8], the most specific signs/symptoms associated with hypogonadism include (1) incomplete sexual development, (2) decreased libido, (3) erectile dysfunction, (4) breast discomfort, (5) loss of body hair, (6) small (<5 ml) testes, (7) oligo/azoospermia, (8) low bone mineral density, and (9) hot flashes or sweats. Nevertheless, many of these sequelae may be associated with other disorders or have no unifying causal link. To improve diagnostic accuracy, numerous professional societies recommend a combination of statistical and clinical approaches to diagnose hypogonadism [8–11].

Despite well-executed randomized controlled trials on TRT utilizing rigorous criteria for diagnosing hypogonadism, considerable controversy remains over the balance of risks and benefits, its applicability to the general population, and ethics surrounding treatment for nonpathological symptoms associated with normal aging (commentary on [12–14]). Although there is a lack of consensus among medical professionals, the preponderance of evidence suggests that TRT prescriptions have risen over the last 2 decades [2]. The objective of this systematic review is to appraise all available evidence on testosterone therapy assuming a marketing viewpoint: assessments of the market size, economic costs associated with hypogonadism, trends in TRT prescriptions, drug discontinuation rates, and advertising and sales efforts in the USA.

2. Evidence acquisition

2.1. Data sources and searches

We performed a systematic review to review major studies on marketing and testosterone in the USA according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses system [15]. PubMed, Embase, and Scopus databases were utilized. The search strategy (Supplementary material) was adapted and updated by a health sciences librarian (C.B.W.). The PubMed and Embase searches were from 1964 to present and 1974 to present, respectively. The search strategy was combined with a search string representing concepts in marketing and testosterone therapy. These include Medical Subject Headings (MeSH) and their descendant MeSH terms along with natural language terms. See the Supplementary material for further details on search strategies for each respective database.

2.2. Study selection

We limited our search articles to the English language. We included only primary testosterone marketing research articles. Studies on market size, prescription patterns, direct-to-consumer marketing, Internet marketing, and economic cost analyses were included. We excluded non-primary studies, non-US studies, non-English studies, non-marketing studies, commentaries, review articles, meta-analyses, incomplete abstracts, and studies on serum testosterone levels that did not include treatment for hypogonadism. Articles were initially screened based on a review of title and abstract text. Among the remaining articles, we reviewed the full text and once again applied the screening criteria. References contained within the full-text articles were similarly screened and included in the study if applicable.

2.3. Data collection and data extraction

Parameters on hypogonadism market size, costs of hypogonadism, trends in testosterone prescriptions, long-term compliance with testosterone, and sales and marketing efforts were extracted from studies where applicable.

2.4. Risk of bias assessment

We assessed the risk of bias for each individual study and the screening process as a whole. The Cochrane Risk of Bias reporting system was utilized to assess selection, performance, detection, attrition, reporting, and other bias according to "low," "high," or "uncertain" categories [16].

2.5. Data synthesis

Methodological and clinical heterogeneity of the included studies meant that meta-analysis was inappropriate. Therefore, a narrative synthesis of the data was performed and ranges are provided for data where applicable. Although formal subgroup analyses were not possible due to inclusion of nonrandomized or comparative studies, studies comparing the USA with other countries were highlighted for the purposes of assessing differences in direct-to-consumer marketing versus other forms of marketing.

3. Evidence synthesis

3.1. Screening characteristics

The search was performed on July 28, 2017. A total of 2826 abstracts were queried. Of these, 844 duplicates were removed due to overlap in the databases, resulting in 1982 abstracts; 288 were excluded due to non–peer-reviewed abstracts presented at conferences and 1691 met the screening criteria. Two reviewers collectively screened

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