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Overselling hysteria, dangerously: the media coverage of testosterone therapy in men

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Thesis

**OVERSELLING HYSTERIA, DANGEROUSLY: THE MEDIA COVERAGE OF
TESTOSTERONE THERAPY IN MEN**

by

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Master of Science

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ABSTRACT

Testosterone has been used therapeutically for over 70 years in men suffering from the symptoms of testosterone deficiency (TD, hypogonadism), and a strong body of evidence suggests testosterone treatment is safe and efficacious in patients for whom it is indicated. Additionally, there exists sufficient data to recognize male hypogonadism as a risk factor for cardiovascular disease. Four recently published studies suggested that testosterone therapy is associated with myocardial infarction, stroke, and death. Although these studies are afflicted with poor study design, flawed data analysis and misinterpretations, and received nearly unanimous rejection by experts in the field, the mainstream media has catapulted the studies into the public spotlight with sensationalist headlines, creating a hysteria that has had far-reaching and dangerous implications for patients and physicians. The media-driven hysteria has created an environment in which pharmaceutical companies are being sued, physicians are withholding treatment from men suffering from testosterone deficiency, and the United States Food and Drug Administration has been petitioned to place a black box warning on testosterone products. The imbalanced media coverage has crossed a grave ethical line by interfering in the patient-physician relationship to the extent that patients are being harmed.

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LIST OF ABBREVIATIONS

ASG	Androgen Study Group
DTCA	Direct to Consumer Advertising
Bio-T	Bioactive Testosterone
BLSA	Baltimore Longitudinal Study on Aging
BMI	Body Mass Index
FDA	Food and Drug Administration
FRS	Framingham Risk Score
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin Releasing Hormone
LH	Luteinizing Hormone
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
MOAS	Modified Overt Aggression Scale
NYT	New York Times
PDE5I	Phosphodiesterase 5 Inhibitor
PWS	Prader-Willi Syndrome
SHBG	Sex Hormone Binding Globulin
TOM	Testosterone in Older Men with Mobility Limitations
TD	Testosterone Deficiency
TT	Total Testosterone

INTRODUCTION

The humble beginnings of testosterone research date back to 1849, when Arnold Berthold, a German zookeeper, experimented with rooster castration and testicular re-implantation¹. He determined that some substance secreted by the testis into the blood gave roosters their biologically male characteristics. From that point on, other animal studies and forms of human self-experimentation began to appear sporadically in the medical literature in an attempt to identify and utilize this substance. In 1920, physiologist Eugene Steinach devised a surgical procedure to treat the symptoms that what would later be recognized as those of testosterone deficiency². The “Steinach operation” comprised a unilateral vasectomy, which Steinach posited would shift the functional balance of the testes away from spermatogenesis and toward increased hormone production. Although the benefits of the procedure were never substantiated, Steinach’s work represents one of the earliest interventions designed to treat hypogonadism.

The tale of what is perhaps the most significant breakthrough in the field of male sex hormones occurred shortly thereafter and was recently reviewed in spectacular detail by Freeman et al². To summarize, Adolf Butendant, a German chemist, isolated a male sex hormone from the urine of policemen in 1931³. He identified this hormone as andosterone, and a Swiss chemist named Leopold Ruzicka devised a method to synthesize it in 1934². After a Dutch group

published a paper identifying testosterone in early 1935⁴, Butendant and Ruzicka simultaneously published papers describing methods for preparing synthetic testosterone. The two researchers were offered the Nobel prize for chemistry in 1939 for their groundbreaking work².

In 1940, Dr. Joseph Aub published a report on medical progress in the New England Journal of Medicine reviewing all data available at the time relating to the therapeutic use of testosterone. He concluded, "From this report of the practical use of testosterone in clinical medicine it is obvious that the drug is a potent one, particularly in hypogonadism in males. In this condition its effectiveness as substitution therapy is uniformly accepted."⁵ Then, in 1943, Aub and his colleague Dr. Seymour Kety published another paper detailing the advances in testosterone therapy during the intervening three years⁶. The evidence presented in this article strengthened the argument for testosterone substitution therapy in male hypogonadism, and suggested that the hormone may have beneficial effects in many other diseases.

Also in 1943, Dr. Maurice Lesser experimented with the testosterone propionate ester as a treatment for angina pectoris⁷, or chest pain caused by coronary heart disease. He treated 46 patients, 41 men and 5 women, who suffered from the syndrome with a single 25 mL injection every 2-5 days for an average of 11 injections, and compared the results to those of a control group receiving injections of plain sesame oil. Lesser reported in the New England Journal of Medicine, "The frequency, severity and duration of attacks were

diminished, and all patients were able to increase their physical activity considerably without precipitating an attack of pain.”⁷. In many patients, he also observed lower blood pressure. Interestingly, these favorable effects persisted for 2-12 months after the testosterone treatment was stopped.

Based largely on the work of Aub and Lesser, the United States Food and Drug Administration approved testosterone therapy for the treatment of hypogonadism in men in the 1950s⁸. For the better part of the past century, testosterone therapy has continued to offer a host of benefits to millions of men suffering from testosterone deficiency.

Recently, however, testosterone therapy and its proponents have moved into the crosshairs of the mainstream media. Fueled by four studies linking testosterone therapy to cardiovascular disease that have been unanimously rejected by the scientific community, newspapers and television outlets have created a culture of hysteria and fear surrounding this legitimate medical treatment that has been studied for over 150 years. This unethical coverage has had widely applicable consequences, including unwarranted lawsuits against the pharmaceutical industry and physicians withholding treatment from their patients. This review aims to objectively evaluate the methodology and conclusions of these four studies, compile and summarize other literature relevant to the topic, examine the themes consistently present in the media’s coverage, discuss the far-reaching implications of the hysteria, and determine why testosterone therapy is an easy and interesting target that journalists know will drive readership.

ESSENTIAL PHYSIOLOGY

Testosterone Deficiency and Testosterone Therapy in Hypogonadal Men

Simply put, hypogonadism is symptomatic testosterone deficiency. More specifically, the Endocrine Society⁹ recommends “making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels.” The authoritative organization places the lower limit of the normal range for total testosterone at ~300ng/dL, and enumerates the symptoms and signs as shown in table 1⁹. According to the European Association of Urology guidelines on male hypogonadism¹⁰, there are three classifications of the syndrome:

- Primary hypogonadism is caused by a testicular abnormality that results in failure to produce adequate levels of testosterone.
- Secondary hypogonadism reflects a defect in the pituitary gland or hypothalamus, affecting levels of tropic hormone (GnRH) and/or gonadotropin (LH and FSH).
- Combined hypogonadism involves defects affecting both the gonads and endocrine glands.

To distinguish between the three, clinicians are advised to measure serum LH and FSH. In primary hypogonadism, there is very little testosterone available to regulate secretion the pituitary gonadotrophs via the negative feedback loop, so FSH and LH levels will be elevated. Conversely, in secondary hypogonadism, defects in the hypothalamus and pituitary cause decreased levels of FSH and

LH. In combined hypogonadism, the serum LH and FSH levels will vary according to which cause is more prevalent.

A. More specific symptoms and signs

- Incomplete or delayed sexual development, eunuchoidism
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small (especially <5 ml) or shrinking testes
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats

B. Other less specific symptoms and signs

- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance

Table 1. Symptoms and signs suggestive of testosterone deficiency in men.[Taken from the Endocrine Society Clinical Practice Guideline Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes⁹].

Klinefelter's syndrome, varicoceles, chemotherapy, orchitis, environmental toxins, and various other rare genetic conditions can underlie primary hypogonadism. Radiation exposure, trauma, pituitary adenomas, certain medications, sleep apnea, diabetes mellitus, chronic kidney disease, infection, hypothyroidism, Kallman syndrome, and Prader-Willi syndrome may contribute to secondary hypogonadism¹¹.

A strong body of evidence, established as early as 1958¹²⁻²¹ supports the idea that the incidence of androgen deficiency increases as men age. Serum testosterone levels have been reported to decrease by 0.4-2.0% per year²¹⁻²⁴.

Importantly, the Baltimore Longitudinal Study on Aging (BLSA)²⁴, a longitudinal study of 890 men with a mean age of 58.8 ± 15.8 , found 19% of men over the age of 60, 28% of men over 70, and 49% of men over age 81 had total serum testosterone levels below the reference range. Additionally, the BLSA showed that sex hormone binding globulin (SHBG), a protein that binds and inactivates androgens in the blood, increases at a rate of 1.2% per year. Free, or bioavailable, testosterone also decreases with age (see figure 1).

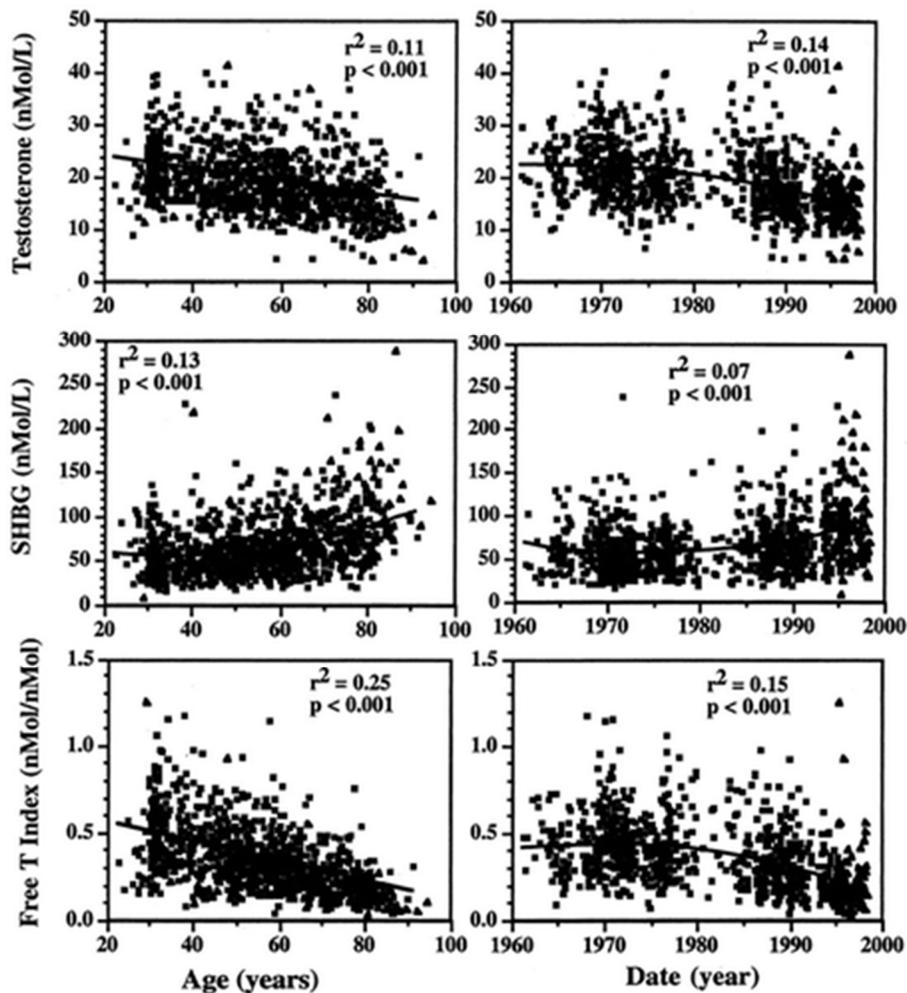


Figure 1. Effects of age (left panels) and date (right panels) on serum T, SHBG, and free T index [Taken from Harman et al.²⁴]. Top row: Total testosterone levels tended to decrease as the men aged. The curvilinear regression in the top left panel suggests total testosterone drops at faster rate in elderly men than in younger men. Middle row: SHBG concentrations correlate positively in a curvilinear manner with age. The observed rate of increase was greater in older men than in younger men. Bottom row: Like total testosterone, free testosterone levels decreased with age in a curvilinear pattern, decreasing at a greater rate in older men than in younger men.

As reviewed by Kaufman and Vermeulen²², there are three primary mechanisms by which this condition, referred to as late-onset hypogonadism or andropause, occurs:

First, the male gonads undergo primary changes such that the number of Leydig cells decreases, reducing the testicular secretory capacity²⁵. This finding is consistent with the lower testicular volume observed in older men²⁶. Furthermore, animal studies suggest that enzymes involved in steroidogenesis diminish with age²⁷.

Second, aging correlates with an alteration in the hypothalamic control of Leydig cell function. As men age, serum LH levels increase modestly²⁰, likely due to decreased metabolic clearance²⁸. However, it is not the mean serum levels, but the pulsatile LH secretion that governs Leydig cell function. These pulses, elicited by GnRH, diminish in magnitude in the elderly²⁹. Thus, it may be that the alteration in neuroendocrine control of the Leydig cells is seen at the level of the hypothalamus.

Third, as mentioned in the BLSA²⁴, SHBG levels increase as men age, resulting in lower levels of free testosterone. Normally men compensate for an increase in SHBG and maintain free testosterone levels by increasing gonadal testosterone production, but, as discussed, there is diminished Leydig cell secretory capacity in the elderly.

Testosterone Therapy and Cardiovascular Disease

It is well established that testosterone plays an important role in erectile function, libido, energy, bone density, and maintenance of lean body mass. Interestingly, there is data to suggest that testosterone may protect against cardiovascular disease and all-cause mortality, and untreated testosterone deficiency should absolutely be recognized as a risk factor for cardiovascular disease. As discussed, testosterone was used successfully as early as 1943 to treat angina pectoris⁷.

In 2006, Shores et al. published a novel study correlating low testosterone levels to increased mortality in a population of 858 male veterans³⁰. In a 2010 prospective study of 930 men with coronary artery disease, Malkin et al. confirmed this finding by reporting that four parameters impacted the time to all-cause mortality: left ventricular dysfunction, aspirin therapy, β -blocker therapy, and low serum bioactive testosterone. In their discussion, the authors state, "low endogenous bio-T is related to all-cause and vascular mortality in a coronary disease population. TT is weakly associated with survival and a cut-off of TT of less than 15.1 nmol/l is related to increased mortality. Therefore, we also

conclude that borderline low levels of TT may also adversely impact on survival.”³¹ These two studies are supported by several others^{32–38} in their findings. Additionally, in a study of 308 men with sexual dysfunction, Lee et al. reported a significant negative correlation between total testosterone levels and cardiovascular risk as, stating in their conclusion, “high testosterone level may decrease the risk of cardiovascular disease.” Yeap et al.³⁹ corroborated these findings in a study of 3,690 men over the age of 70, reporting that a higher plasma testosterone level is a biomarker for reduced risk of stroke.

As reviewed by Traish⁴⁰, testosterone deficiency may pose numerous other cardiovascular related dangers to those who suffer from it, including dyslipidemia¹⁹, endothelial dysfunction⁴¹, and hypertension⁴².

Clearly, the overwhelming majority of the available data suggests testosterone levels negatively correlate to adverse cardiovascular events: hypogonadal men are at a higher risk for cardiovascular disease than eugonadal men. Unsurprisingly, there is also evidence that testosterone therapy in hypogonadal men may reduce the incidence of cardiovascular disease. Recently, Baillargeon et al. examined a large cohort from a database of Medicare beneficiaries and found “Older men who were treated with intramuscular testosterone did not appear to have an increased risk of MI. For men with high MI risk, testosterone use was modestly protective against MI.”⁴³ In a large observational study of 934,283 men, Etminan et al.⁴⁴ found no association between past or current testosterone therapy and myocardial infarction.

Similarly, Tan et al. found “no evidence of worsening preexisting MI or stroke in patients treated with testosterone.” in a cohort of 39,936 men⁴⁵.

Within the past five years, four studies have been published^{46–49} correlating testosterone therapy in men to cardiovascular risk: a prematurely-terminated clinical trial, a meta-analysis, and two retrospective observational studies. It will be made clear in this review that these studies are fraught with methodological and experimental design problems, data mismanagement, as well as a myriad of statistical complexities with more variables and extrapolations, which makes analysis and interpretation of such data very difficult; notwithstanding, the mainstream media has selfishly and irresponsibly rendered in the public eye the idea that these four studies represent irrefutable truth and that the pharmaceutical industry has medicalized a normal aspect of aging for the sake of profit. The perpetuation of these myths on the front pages of national and regional newspapers and on various social media outlets has had several unfortunate consequences, including physicians halting treatment of a legitimate medical condition, unwarranted class action lawsuits against healthcare providers and drug manufacturers, a call for the FDA to place a black box warning on testosterone products, and a witch hunt directed against proponents of testosterone therapy.

STUDIES CLAIMING A LINK BETWEEN TESTOSTERONE AND CARDIOVASCULAR DISEASE

On February 25, 2014, the consumer advocacy organization Public Citizen officially petitioned⁵⁰ the Food and Drug Administration (FDA) to “add a black box warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all testosterone containing drugs presently on the market in the U.S... [and] to ask manufacturers to send “Dear Doctor” letters to warn physicians of these serious adverse effects”. This petition was subsequently denied by the FDA⁵¹, but an examination of the evidence it contains is useful to gain an appreciation for what little evidence exists linking testosterone to cardiovascular problems.

To support their argument, the petitioners cited four noteworthy studies^{46–49}. Despite contradicting a strong body of evidence spanning a decade suggesting testosterone therapy is safe and may have cardiovascular benefits^{30,32,33,52,35,34,53,54,38,55,56,37,57,31,58,59,36,60–63}, these four studies have received a disproportionate amount of favorable media coverage. In the following sections, we will examine the four studies and the coverage they have received, discuss the implications for patients and physicians, and explore why testosterone therapy has become such a hot-button issue in the mainstream media.

Basaria et al., *Adverse Events Associated with Testosterone Administration.* (NEJM 2010)⁴⁶

The first paper indicating a significant increase in cardiovascular risk associated with testosterone therapy was published in 2010 by Basaria et al. in the New England Journal of Medicine. The study, referred to as the Testosterone in Older Men with Mobility Limitations (TOM) trial, was designed to evaluate the effects of testosterone therapy in hypogonadal men over the age of 65 with evidence of limitations in mobility. The cohort comprised 209 men who had a total serum testosterone level between 100 and 350 ng/dL or a free serum testosterone level of less than 50 pg/mL. A portion of the men were randomly assigned to daily application of a testosterone gel (n=106), and the remaining men were assigned a placebo gel (n=103). However, the trial was aborted just four years after enrollment began because a data and safety monitoring board determined a significantly higher incidence of cardiovascular-related events in the group receiving testosterone gel as compared to the placebo group.

Although the premature results of the Basaria study are ostensibly troubling, the authors' study design, analysis, and conclusions have been categorically refuted by the FDA and expert academicians in the field of testosterone therapy. Indeed, for the reasons explained below, the title of this publication is misleading, inappropriate, and inaccurate.

In response to the Public Citizen black-box petition, the FDA wrote, "the Basaria study... had several significant limitations that precluded a definitive assessment in the role of testosterone therapy in cardiovascular events noted in the study"⁵¹. Indeed, Basaria et al. admitted, "the lack of a consistent pattern in

these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone.”⁴⁶ When the FDA examined only major adverse cardiac events (MI, stroke, and death due to MI or stroke), they found only an insignificantly small imbalance in the incident of events between the testosterone and placebo groups⁵¹. Furthermore, the randomized groups were not balanced for preexisting cardiovascular risk factors.

In their discussion of a potential mechanism for testosterone to increase cardiovascular risk, Basaria et al. mention that “the use of anabolic steroids has been associated with left ventricular hypertrophy.” The two studies^{64,65} cited to substantiate this assertion are wholly irrelevant to the matter of testosterone treatment in hypogonadal men. From the title of the both references, it is clear the publications addresses only the chronic misuse of anabolic steroids. The second cited⁶⁵ study found that effect is potentiated by concomitant use of growth hormone, further distancing its results from those of the Basaria study.

The Endocrine Society Clinic Practice Guidelines⁹ recommends a regimen of 5-10g of 1% testosterone gel containing 50-100mg applied daily. The testosterone group in the TOM trial was started on the maximum recommended dose, 10g of transdermal gel containing 100mg of testosterone applied once per day, and the dose for some participants was increased to 15g during the course of the study. The authors caution against “extrapolating these findings to other

doses and formulations”⁴⁶, which would include all submaximal doses recommended by the Endocrine Society.

Importantly, as described in the trial design and methods publication from March 2009⁶⁶, the primary objective of this study was “determine whether testosterone therapy in older men with low testosterone levels and mobility limitations will increase maximal voluntary muscle strength as measured by the 1 repetition maximum.” In fact, assessing cardiovascular outcomes was completely omitted from the initial trial design publication. Thus, there existed a severe limitation regarding the ascertainment of the cardiovascular events.

Xu et al., Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. (BMC 2013)⁴⁷

The Public Citizens petition also adduces an April 2013 meta-analysis of 27 placebo-controlled randomized trials of testosterone therapy in men that reported cardiovascular events. The meta-analysis evaluated 2,994 men, 1,733 of whom received testosterone therapy and 1,261 of whom received placebo, treated for 12 weeks between 1986 and 2012. Overall, Xu et al. reported a 54% higher incidence rate of cardiovascular-related events in the testosterone groups as compared to the placebo groups. Specifically, in studies not funded by the pharmaceutical industry, they found a two-fold increase in the incidence of cardiovascular events in the testosterone group.

The FDA pointed out several methodological issues in the design and execution of the 27 component studies, such as inappropriately broad definitions of cardiovascular-related events that included hypotension, bleeding esophageal varices, syncope, and peripheral edema⁵¹. They also suggested the discrepancy in outcomes based on funding source may have been due to chance.

In a commentary on the Xu study, Morgentaler et al.⁶⁷ determined that 2 of the 27 trials included in the meta-analysis accounted for a disproportionate 35% of the reported cardiovascular related-events. The first of these two studies was conducted in 1986 and examined the effects of supraphysiological doses of an oral testosterone formulation in men with alcoholic cirrhosis⁶⁸. Ironically, the Endocrine Society recommends against the use of orally-active testosterone due to hepatotoxicity of the compounds⁹. For this reason, it is inaccurate to extrapolate the 16 cardiovascular events reported in the 1986 study testosterone group to the treatment of hypogonadal men with approved testosterone formulations. The second study⁴⁶, published by Basaria et al. in NEJM and addressed earlier in this section, is rife with severe limitations.

The primary data from this meta-analysis demonstrate that there were 6.6 reported cardiovascular-related events per 100 men in the testosterone group, as compared to 5.2 in the placebo group. The modesty of this asymmetry alone is enough to reject Xu et al.'s conclusion that testosterone therapy increases cardiovascular-related events among men. Moreover, if the two outlier trials mentioned previously^{46,68} are removed from the primary data, the incidence of

cardiovascular events in the testosterone group falls to 4.9 events per 100 men in the group treated with testosterone, versus 5.1 events per 100 men in the placebo group.

Vigen et al., *Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels.* (JAMA 2013)⁴⁸

In early November 2013, a group from the University of Texas and University of Colorado led by Rebecca Vigen published a study in the Journal of the American Medical Association (JAMA) titled *Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels*. The study aimed to identify whether an association between testosterone therapy and mortality, myocardial infarction, and stroke existed in a retrospective cohort of hypogonadal men who underwent coronary angiography from 2005 to 2011 in the Veterans Affairs system. Ostensibly, the authors reported a significantly higher 25.7% risk of cardiovascular events in the group receiving testosterone therapy three years after the coronary angiography, as compared to 19.9% in the control group. Delving deeper into the study's statistical analysis, it is clear that the raw data was grossly misrepresented.

First, the statistical analysis was accomplished using stabilized inverse propensity treatment weighting (IPTW) applied to a Kaplan-Meier estimator with testosterone therapy as a time-varying covariate. In a paper published in January 2012 by Michael P. Ho⁶⁹, senior author of the Vigen et. Al study, he

admitted the methodology is “challenging and needs further study.”⁶⁷. Just two months after the JAMA was published, an official correction⁷⁰ was issued, altering the wording to demonstrate the complexity of the statistical methodology.

Second, the authors adjusted for 57 variables, but failed to adjust for serum testosterone measured at baseline⁷¹. In a study by Lee et al.⁷², higher serum testosterone levels were associated with a lower Framingham Risk Score, a predictor of 10-year cardiovascular outcome risks (see figure 2). In the Vigen et al. study, the group that did not receive testosterone therapy had a mean baseline total testosterone level of 206.5ng/dL, versus 175.5ng/dL in the group receiving testosterone. Extrapolating the findings from Lee et al. to the Vigen et al. study, it would be expected that the no treatment group would have better cardiovascular outcomes regardless of treatment.

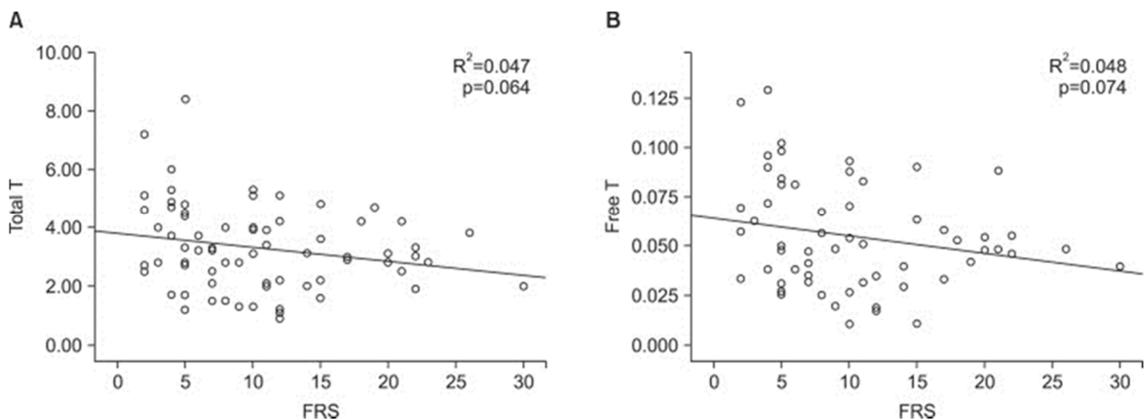


Figure 2. Representation of correlation analysis between testosterone levels and FRS

[Taken from Lee et al⁷²]. Panel (A) depicts a negative correlation between adverse cardiovascular outcomes as represented by the Framingham Risk Score (FRS) and the total

testosterone level. Panel (B) suggests a negative correlation between the FRS and the free testosterone levels.

Third, in an invited commentary published in *The Journal of Sexual Medicine* in response to the *JAMA* article, Traish et al.⁷¹ reexamined the raw data from the study, stripping away the layers of complex statistical masking, and found that there was actually a lower rate of cardiovascular events in the group receiving testosterone therapy (see Figure 3). Additionally, Shores et. al³⁰ reported strikingly similar results in a separate observational study, examining 1031 hypogonadal male patients in the Veterans Affairs database. They found a 20.7% mortality in the no-treatment group after 3-5 year, as compared to just 10.3% in the group receiving testosterone therapy. These findings are consistent with a growing body of strong evidence suggesting testosterone therapy has cardioprotective effects⁶⁷.

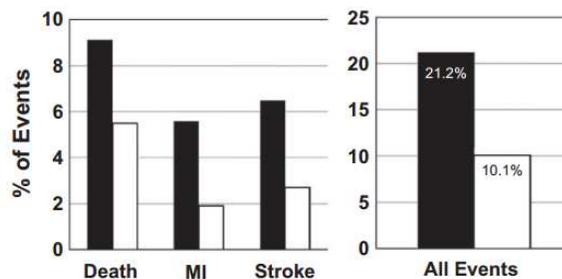


Figure 3. Actual association between cardiovascular events and testosterone therapy in the Vigen et al. study⁴⁸ [Taken from Traish et al⁷¹]. The left graph shows the absolute rate of death, myocardial infarction (MI), and stroke in untreated men (black) and men receiving

testosterone therapy (white) based on the primary data of Vigen et al. The right graph depicts the absolute total event rate of death, myocardial infarction (MI), and stroke in untreated (black) and men receiving testosterone therapy (white), also from the Vigen et al. primary data.

Fourth, Traish et al.⁷¹ discovered that Vigen et al. excluded 1,132 subjects who received testosterone therapy after experiencing an adverse cardiovascular event. The events these men suffered clearly should have been included in the no treatment group. Just one day after the publication of Traish et al.'s commentary revealing this egregious oversight, JAMA issued a second official correction⁷⁰, including 1,004 of the aforementioned men who had previously been excluded. Somewhat comically, it was also disclosed that Vigen et al. had mistakenly included 100 women in the study.

The Androgen Study Group (ASG) is a consortium of clinicians and scientists that formed largely in response to the Vigen et al. article. Their mission, as stated on their website, is “to ensure that the results of research regarding testosterone deficiency and its treatment are presented accurately and fairly within medical literature and to the public.” To date, 29 medical societies and greater than 160 medical professionals⁶⁷ from around the world have signed the ASG petition calling for an official retraction of the Vigen et al. study from JAMA.

Finkle et al., *Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men.* (PLoS One 2014)⁴⁹

In January 2014, a third study purporting an association between testosterone therapy and increased cardiovascular risk was published by Finkle et al. in PLoS One. In a secondary data analysis of a large healthcare database, 55,593 were identified as having filled a prescription for testosterone. The incidence rate of myocardial infarction (MI) in the 90 days following the first testosterone prescription was compared to the MI incidence rate for the year prior to the initial prescription. These same intervals were also compared for 167, 279 men who were prescribed a phosphodiesterase 5 inhibitor (PDE5I), a drug primarily used to treat erectile dysfunction, who served as a control group. Overall, the study reported a 36% increase in the incidence rate of MI in for men who had filled a testosterone prescription, as compared to an 8% increase in men prescribed a PDE5I. Additionally, in men over the age of 65 prescribed testosterone, the MI incidence rate increased by 119%, versus 15% in the PDE5I group. However, this study was severely limited in several aspects.

As this study was merely an examination of diagnoses codes and prescription information, there is no verifiable data available regarding the patients' adherence to the testosterone therapy. There exist three subgroups within the testosterone group based on the endpoints to which they were followed: (1) men who refilled their prescription at least once in the first 90 days and did not experience an MI before the refill, (2) men who went the entire 90 days with neither an MI nor a prescription refill, and (3) men who experienced an MI before refilling their prescription. Although this study does not provide this

information, it is likely that the patients in group 1 were adherent to their prescription and refilled at the typical 30 day point. Conversely, group 2 likely did not adhere to the prescribed treatment as evidenced by their lack of refill. As the study does not provide data regarding how many of the 65 post-prescription MI cases occurred in day 1-30 versus day 31-90, it is unclear whether the patients in group 3 who experienced an MI were adherent to treatment. It is well known that the administration of exogenous testosterone suppresses the gonadal production of endogenous testosterone. Moreover, there is evidence that low serum testosterone is associated with an increased risk of cardiovascular events⁷². Therefore, it is entirely plausible that many of the patients who experienced an MI were noncompliant with their treatment. Theoretically, if the men in group 3 used testosterone briefly and then abruptly discontinued treatment, their serum testosterone would drop to very low levels, increasing their risk for MI.

Moreover, the researchers did not have access to any clinical data. They were unable to adjust for BMI, social history, blood pressure, and blood test values indicative of cardiovascular risk, including baseline serum testosterone or cholesterol.

Lastly, as elaborated by Dupree et al.⁷³ in a published response to the PLoS One study, it was inappropriate to use the patients receiving PDE5I prescriptions as a control group. Sildenafil, more commonly known as Viagra, was discovered in an attempt to treat angina, and is currently indicated in the treatment of pulmonary hypertension. Both of these conditions have severe

cardiovascular implications. Preclinical studies suggest PDE5i may protect against MI, ischemia/reperfusion injury, cardiotoxicity of certain medications, and heart failure^{74,75}. Additionally, a recent meta-analysis found that PDE5I may have cardioprotective properties in patients with left ventricular hypertrophy (LVH)⁷⁶. Finkle et al. chose PDE5I as a comparison because the drugs “have not been associated with adverse cardiovascular events.”⁴⁹ While true, the authors failed to mention the possible cardiovascular benefits of PDE5I, which may have artificially lowered the number of cardiovascular events observed in the comparison group.

Despite the embarrassingly poor study design, irresponsible data management, distorted statistical analysis, and unanimous repudiation by authorities in various relevant fields, these three articles received an overwhelming amount of media attention.

EVALUATION OF MEDIA COVERAGE

Quick Study: Testosterone supplement may have cardiovascular risks for older men (Washington Post, 2010)⁷⁷

“This study involved 209 men, who averaged 74 years old and had low testosterone levels and mobility problems...They were randomly assigned to apply a testosterone gel (Testim) or a placebo gel daily. After six months, those using testosterone recorded greater improvements in lower-extremity strength and physical functioning. However, twice as many men in the testosterone group were evaluated for a medical problem. This included 23 men who had a cardiovascular problem (including high blood pressure, arrhythmia, stroke and a need for stenting), compared with five men in the placebo group, and seven (vs. one) who had an atherosclerosis-related problem (including heart attack, angioplasty and coronary artery bypass).”

This Washington Post article, reporting the results from the TOM trial by Basaria et al.⁴⁶, marks the first time an academic study linking testosterone therapy to cardiovascular risks appeared in one of the top ten most circulated newspapers in the United States. Aside from not recognizing several of the problems with the Basaria study noted in the previous section, this article was relatively objective and pointed out that the authors conceded "the differences detected between the two trial groups may have been due to chance alone."⁴⁶. This manner of balanced discussion would soon all but vanish in the following articles as testosterone therapy became a popular target for journalists.

Testosterone Treatments Linked to Heart Risk (USA Today, 2013)⁷⁸

“Testosterone treatments may increase risks for heart attacks, strokes and death in older men with low hormone levels and other health problems, a big Veterans Affairs study suggests... Men who used testosterone were 30 percent more likely to have a heart attack or stroke or to die during a three-year period than men with low hormone levels who didn't take the supplements.”

This Associated Press piece published in the USA Today reports on the Vigen study⁴⁸ discussed earlier. As shown, the highly statistical approach and poor data management to this study has resulted in its unanimous rejection by experts in the field.

Overselling Testosterone Dangerously (New York Times, 2014)⁷⁹

“A large study has found substantial risks in prescribing testosterone to middle-age and older men for a variety of ailments. One part of the study found that testosterone doubled the risk of cardiovascular disease in more than 7,000 men who were 65 years old or older, essentially confirming findings in previous studies. The other part found that testosterone almost tripled the risk of heart attacks in a group of more than 48,000 middle-age men with previous histories of heart disease. The harm in both cases occurred within 90 days of receiving the prescription... Drug companies have shamelessly pushed the notion, to doctors and to the public, that their testosterone-boosting product can overcome a supposed disease called “low T,” which is characterized by feelings of fatigue, loss of sexual drive, depressed moods, an increase in body fat and decrease in

muscle strength, among other symptoms... Men need to recognize the dangers of seeking a quick fix for aging, and doctors need to be more cautious in prescribing.”

The scornfully succinct editorial begins by summarizing the reported results from the Finkle et al. study⁴⁹ addressed earlier, touting it as *“the most compelling evidence yet that many American men have embarked on a perilous course of overtreatment.”* As we have shown, the Finkle study was gravely limited, which is why the FDA rejected it as insufficient evidence for a black-box warning, stating, “it is difficult to attribute the increased risk for non-fatal MI seen in the Finkle study to testosterone alone”⁵¹.

The NYT piece also reported that *“in a striking comparison, it found that drugs used to treat erectile dysfunction, such as Viagra and Cialis, which are often prescribed for similar purposes, did not increase heart risks.”* As previously explained, this finding is the antithesis of ‘striking.’ Based on a wealth of evidence available to the authors, this mundane finding would be expected by any scientifically literate individual who read the methods section of the study. However, as none of the 19 members of the NYT Editorial Board has a formal education in science, it may indeed have been shocking to them.

Lastly, there is no doubt that aging is associated with decreasing testosterone levels²², but that certainly does not mean it should be shrugged off as part of the aging process and not treated. Macular degeneration is associated with aging, yet it is treated with anti-angiogenic drugs and laser therapy⁸⁰;

hypertension is associated with aging, yet it is treated with a vast array of drugs⁸¹; type 2 diabetes is associated with aging, yet it is treated with hormone therapy and other drugs⁸²; hearing loss is associated with aging, yet it is treated with hearing aids and cochlear implants⁸³; hyperlipidemia is associated with aging, yet it is treated with some of the most frequently prescribed drugs on the market⁸⁴; osteoporosis is associated with aging, yet it is treated with vitamin and mineral supplementation and several medications⁸⁵; rheumatoid arthritis is associated with aging, yet it is treated with steroids, biologics, and surgery⁸⁶; gastroesophageal reflux disease is associated with aging, yet it is treated with H-2-receptor blockers and proton pump inhibitors⁸⁷; urinary incontinence is associated with aging, yet it is treated with anticholinergic drugs and surgery⁸⁸. Just because a medical condition is associated with age, it does not follow that it should not be treated. Unfortunately, some licensed physicians in the United States have opened “anti-aging clinics,” relying on testosterone, human growth hormone, and thyroid hormone therapy to make their clients feel younger. At this time, there is insufficient evidence to use testosterone therapy as “a quick fix for aging” in and of itself. Such clinics represent irresponsibly practiced medicine and reflect poorly on board-certified endocrinologists, urologists, and primary care physicians who administer testosterone therapy responsibly to hypogonadal men.

Don't Ask Your Doctor About 'Low T' (New York Times, 2014)⁸⁹

Just one day before *Overselling Testosterone, Dangerously* hit the pages of the New York Times, the newspaper published an Op-Ed from internist Dr. John La Puma, also highlighting the Finkle Study⁴⁹. He proceeded to make several claims regarding testosterone therapy that are not supported by scientific evidence:

*“In addition to the cardiac risks, prescription T can mean a permanent shut-off in men’s own, albeit diminished, testosterone production.”*⁸⁹ This assertion is simply not true. To our knowledge, there has never been a documented case of testosterone therapy irreversibly inhibiting the HPG axis. Additionally, hypogonadism is not a disease that spontaneously corrects itself; testosterone is intended as a lifelong treatment, and any physician who has read best practice guidelines will discuss this with patients before initiating therapy.

*“Instead of heading to the pharmacy to get their fix, men should address the leading cause of the problem. Losing weight is a tried and true way to naturally boost testosterone levels.”*⁸⁹ With the heterogeneity in clinical presentation of hypogonadism, it is absurd to attribute the majority of cases to high body fat. While it may be true that the majority of hypogonadal men are overweight⁹⁰, evidence has shown that testosterone therapy in these men produces sustained weight loss⁹¹. Therefore, in this chicken-and-the-egg scenario, it is likely that low serum testosterone contributes to obesity more significantly than obesity contributes to low serum testosterone.

“The last thing they need now is a prescription for a risky drug to treat a trumped-up disease.” Amusingly, Dr. La Puma is the author of a book titled “Refuel: A 24-Day Eating Plan to Shed Fat, Boost Testosterone, and Pump Up Strength and Stamina.” As a board-certified internist, one would assume that he recognizes hypogonadism as a legitimate disorder on some level, rather than a simply “trumped-up disease.” However, it seems that he would prefer to steer readers’ money away from prescription copays and into his own pocket through the purchase of his book, a VIP subscription to his personal website, or his e-commerce store selling various unregulated supplements.

Men’s Use of Testosterone on the Rise (New York Times, 2013)⁹²

“The number of middle-aged men with prescriptions for testosterone is climbing rapidly... a study published in the journal JAMA Internal Medicine found that many men who get prescriptions for the hormone have no evidence of a deficiency at all... a quarter of men did not have their levels tested before they received the hormone.”

This NYT Well Blog article primarily examines a 2013 study by Baillargeon et al.⁹³ on testosterone prescription trends in the United States between 2001 and 2011. Using data from a commercial health insurance database, the study found that testosterone use increased from 0.81% in 2001 to 2.91% in 2011 among men 40 years or older. For reasons that will be discussed at the end of this section, this observed increase is not cause for concern. Additionally, as this cohort included only commercially-insured men over the age of 40 with

employment-based plans, its findings cannot be generalized to younger, retired, or otherwise unemployed men.

The Baillargeon study also reported that 25.28% of men who were prescribed testosterone therapy did not have a serum testosterone measurement recorded in the insurance database. While this finding is troubling and indefensible, it serves only to highlight the need for more balanced discussion and greater education among physicians regarding the diagnosis and treatment of hypogonadism. Indeed, the Endocrine Society⁹ and European Association of Urology recommend confirming the diagnosis of hypogonadism by measuring at least two separate serum samples taken in the morning, when testosterone levels are highest⁹⁴.

Selling That New-Man Feeling (New York Times, 2013)⁹⁵

“This marketing juggernaut is running into mounting opposition from some prominent medical researchers and industry experts. They contend that the pharmaceutical industry has vastly expanded the market for testosterone drugs to many men who may not need them and may be exposed to increased health risks by taking them. And drug makers have done so, these critics say, by exploiting loopholes in federal marketing regulations. Drug makers spent \$107 million last year to advertise the top brand-name testosterone drugs in the United States, according to Kantar Media... Drug makers also promote low-T screening quizzes directly to consumers, Mr. Mack says, in an effort to prompt men to seek testosterone prescriptions from their doctors... The test has also become

controversial. Most of the questions invoke symptoms that are so general that they could apply to many men who are clinically depressed or simply having a bad day — or even to women, says Dr. Adriane J. Fugh-Berman, an associate professor at Georgetown University Medical Center in Washington. “There are tests that everyone will fail — that is the idea,” says Dr. Fugh-Berman”

This account, written by Natasha Singer, echoes concerns raised in several of the aforementioned write-ups. While it is true that testosterone sales have increased in the past years, this growth is not unprecedented. From 2012 to 2013, the amount of testosterone sold in the United States increased by only 0.6%⁹⁶. Indeed, the observed increases and absolute spending on testosterone remain modest when compared to other drugs (see figure 4)^{96,97}. During the same time period, there was 1.6% more prescriptions of all types filled in the US⁹⁷. In contrast, prescriptions for nervous system disorders increased 5.9% and those for contraceptives increased 4.6%⁹⁷. Between 1988-1994 and 2007-2010, the use of antidepressants among adults increased four-fold⁹⁸. Moreover, testosterone does not appear in Schumock et al.’s analysis of the top 15 drugs by expenditures in 2013⁹⁹. Therefore, the growth in testosterone therapy probably reflects a broader trend in prescribing patterns across all medical fields rather than targeted advertising, as the author of the NYT piece suggests.

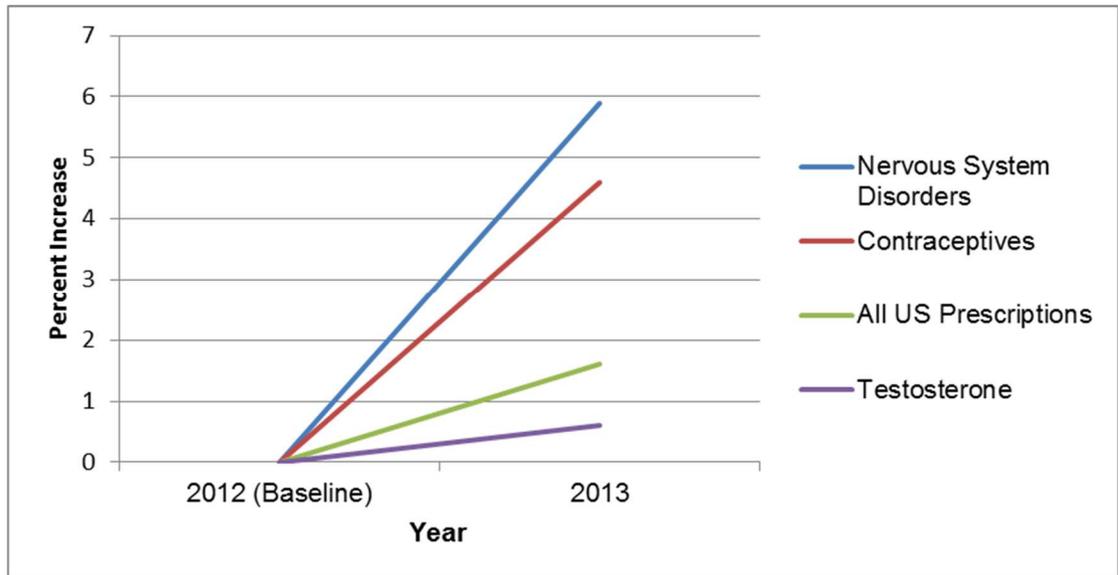


Figure 4. Changes in prescribing rates in the US from 2012 to 2013. As depicted, the increase in testosterone prescriptions is relatively low when compared to medications for nervous system disorders and contraceptives. Additionally, the increase in testosterone prescribing is less than the total increase reported for all US prescriptions. Testosterone data calculated from the Mohamoud presentation⁹⁶. All other data from Aitken et al.⁹⁷

Another explanation for the increase is the development of more convenient testosterone formulations employing transdermal absorption. AndroDerm, a testosterone patch worn on non-scrotal skin, was approved by the FDA for treatment of hypogonadism in 1995. In 2000, the biopharmaceutical company Abbott Laboratories (now known as AbbVie, Inc.) introduced AndroGel 1%. The quick-drying, odorless, clear gel is applied to the shoulders or abdomen once daily. Although the prevalence of needle phobia is difficult to gauge owing to the proclivity of those afflicted to avoid healthcare settings, estimates range from 3.5 to 10% of the population¹⁰⁰. The transdermal formulations offer a

discreet, easy to use alternative to the traditional injections or pellet insertions for those who would otherwise refuse testosterone therapy due to an aversion to needles.

The NYT piece also comments on direct-to-consumer advertising (DTCA) of pharmaceuticals. Although it remains ethically controversial, DTCA is a remarkably powerful tool in tackling under-diagnosis and under-treatment of myriad medical conditions. In 2004, the FDA reported the results of a consumer survey indicating that 23 million people in the US made a medical appointment due to DTCA to address a condition they had never previously discussed¹⁰¹. These findings augment a 2003 study by Weissman et al. , which found a quarter of patients who saw their doctor after seeing DTCA received a new diagnosis, nearly half of which were categorized as a “high-priority” health concern¹⁰². DTCA has also been shown to encourage patient compliance¹⁰³, improve the patient-physician relationship¹⁰⁴, mitigate the stigma associated with certain diseases¹⁰⁵, and make patients more active participants in their healthcare¹⁰⁶. The author’s supposition that DTCA has increased inappropriate testosterone prescribing is very likely false. Whether or not it is true, the assertion that anyone can fail the online quizzes discussed is irrelevant. The quizzes are not a diagnostic tool and the results should be given no bearing by physicians without bloodwork to confirm the diagnosis. Indeed, survey results demonstrate that as low as 2% of patients who saw DTCA asked for and were prescribed the promoted drug¹⁰⁷. Additionally, research shows that 77% of consumers who

discuss the content of DTCA with their doctors are counseled on health and lifestyle changes¹⁰⁷. As low testosterone is not screened for, it is arduous to estimate the exact number of men with hypogonadism. A 1996 FDA survey placed the number at 4-5 million, 95% of whom were not being treated¹⁰⁸. A 2006 study approximated 13.8 million, >90% of whom were not receiving treatment¹⁰⁹. As of 2013, the percentage of untreated men has dropped significantly, but 50-85% of hypogonadal men remain untreated⁹⁶. The successful DTCA campaign for low testosterone is not a nefarious manipulation by the pharmaceutical industry; rather, it has likely played an essential role in getting more hypogonadal men medical treatment for their medical condition.

Singer goes on to imply that the manufacturers of testosterone formulations spend an exorbitant amount on advertising. She states that \$107 million was spent in 2012 to advertise the top brands of testosterone-containing products, which ostensibly seems very high. Although the dollar amount does not include unbranded low testosterone awareness campaigns, it represents just 0.4% of the \$27.4 billion in total the pharmaceutical industry spent on advertising in 2012¹¹⁰. By contrast, Eli Lilly spent \$237 million in 2012 on direct to consumer advertising alone for its anti-depression medication, Cymbalta¹¹¹. DTCA accounted for only 39% of Cymbalta's total advertising budget for 2012¹¹², which means Lilly spent a total of \$610 million across all advertising channels for the drug. To reiterate, a single pharmaceutical company spent nearly six times more money advertising a single anti-depressant than all manufacturers of brand-name

testosterone spent to advertise their various formulations. In fact, the spending on advertising for testosterone pales in comparison to many other drugs (see figure 5)^{112,113}. Testosterone did not appear in the top ten advertised drugs ranked by pharmaceutical industry spending in the first quarter of 2012¹¹⁴.

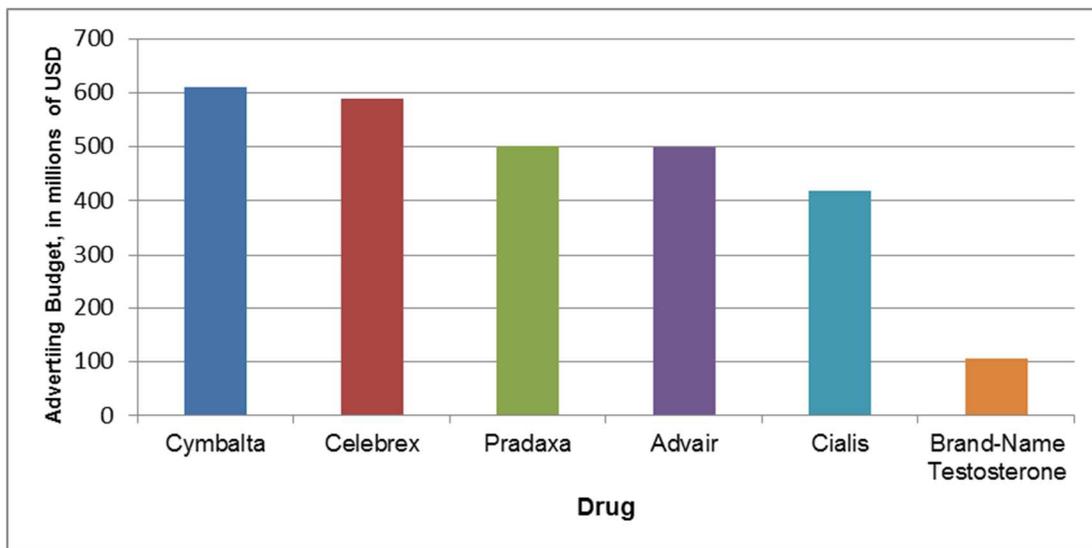


Figure 5. Advertising spending for brand-name pharmaceuticals in 2012. Singer poses the \$107 million spent on advertising by the manufacturers of brand-name testosterone as egregious, but the manufacturers of Cymbalta, Celebrex, Pradaxa, Advair, and Cialis each spent nearly 4-6 times that amount. Data for Testosterone is from the Singer NYT piece⁹⁵. Data for all other drugs calculated from the Cegedim report¹¹² and MM&M report¹¹³.

Testosterone prescription rates have increased in recent years in parallel with, and likely as a result of, the wealth of evidence supporting its efficacy and safety in the treatment of hypogonadal men. Patients are learning that they need not accept low libido, erectile dysfunction, fatigue, and other symptoms severely impacting their quality of life as a normal part of the aging process. Primary care

physicians are learning to include hypogonadism in the differential diagnosis for these symptoms, order the appropriate tests, and refer to suitable specialists. Academicians are learning that testosterone therapy may have a surfeit of beneficial effects for hypogonadal men, including kidney health³⁶, cardioprotective properties⁷¹, and cognitive improvement¹¹⁵. The prescriptions patterns of testosterone-containing product are not the consequence of a misleading advertising campaign by the pharmaceutical industry; rather, they are the culmination of 150 years of research, and represent a change in the landscape of healthcare allowing millions of men live a happier, healthier life.

IMPLICATIONS OF THE MEDIA COVERAGE

The publicity garnered by the four publications linking testosterone therapy to cardiovascular risk has had far-reaching implications.

In June 2014, the US Judicial Panel on Multidistrict Legislation established coordinated proceedings in the federal court circuit to consolidate all class action lawsuits brought against the manufacturers of testosterone formulations before one judge, the Honorable Matthew F. Kennelly. As of December 23, 2014, there were over 700 total actions pending¹¹⁶. Ambulance-chasing lawyers have started buying television and radio advertisements in an attempt to recruit even more potential clients.

Recently a member of the mainstream media attempted to tarnish the reputations of several clinicians and researchers for no other reason than their advocacy of balanced discussion regarding testosterone therapy. In a potentially libelous Wall Street Journal piece¹¹⁷, Ed Silverman accused the Androgen Study Group of attempting to manipulate the results of a NEJM poll¹¹⁸. The poll comprised a vignette describing a 61 year old male presenting with at least three clinical symptoms of hypogonadism and two early-morning serum testosterone measurements to confirm the diagnosis, presented two opposing expert opinions, then asked readers to vote whether or not they would recommend testosterone therapy. The members of ASG sent an email to a limited number of their colleagues encouraging them to read and participate in the poll. When Silverman became aware of the email, he misreported the details and highlighted

the fact that some members of ASG have received food, beverages, and speaking fees from manufacturers of testosterone products. This manner of compensation is innocuous and commonplace; indeed, pharmaceutical companies need input from physicians in order to address the needs of patients, and physicians should be compensated for their time. However, Silverman's article implied the actions of the ASG were nefarious and unprecedented.

The threat of a malpractice lawsuit or attacked by the media is enough to make most clinicians rethink their practices. Many physicians who have caught wind of the ongoing testosterone liability litigation may be reluctant to treat hypogonadal men; that is, an approved medical treatment is probably being withheld from patients with a legitimate medical condition due to fear mongering initiated by the mainstream media and exploited by attorneys. A 2014 survey found that only 9.8% of primary care physicians and cardiologists would refer a patient with testosterone deficiency to a urologist¹¹⁹.

FACTORS UNDERLYING THE MEDIA BIAS

Clearly, physicians and researchers who are in favor of the responsible use of testosterone therapy for the treatment of hypogonadism are being lambasted by the media for simply basing their practice on the best evidence available. But why does this discrepancy exist? As discussed, testosterone has been used medically for nearly a century. What kindling did journalists see in the realm of testosterone therapy that they could use to light the fire of hysteria, and why did they choose now to launch the attack?

Controversy

Controversy, in the dichotomous sense, can be defined as a single set of evidence interpreted two different ways to yield two opposing conclusions. Clearly, the media thrives on controversy: Should the United States be at war? Should this candidate be elected? Should this person be found guilty of an alleged crime? People are emotionally invested in these topics, and without appealing to that connection through stories of this type, newspapers would lose a large portion of their readership.

Testosterone therapy differs from these examples in that there is little controversy surrounding it within the medical community; the overwhelming majority of clinicians and researchers familiar with the literature have rejected the conclusions of the four studies purporting a connection between testosterone therapy in hypogonadal men and cardiovascular risk⁴⁶⁻⁴⁹. In this case, the media did not just write about a controversy: they created one.

Abuse of Anabolic Androgenic Steroids

Of concern to medical professionals is the potential for misuse of exogenous androgens for the purposes of sports performance enhancement, a practice especially prevalent in many bodybuilding and powerlifting circles. There is undoubtedly a dose-dependent relationship in men between testosterone levels and the ability to gain lean muscle mass¹²⁰. However, little evidence exists to support the safety of exogenous testosterone administration in eugonadal (T > 300 ng/ml) men or supra-physiological dosing in any gonadal state. Moreover, there are many published case studies involving irresponsible anabolic steroid use associated with disease state, including toxic hepatitis¹²¹, bile acid nephropathy¹²², cardiomyopathy, and ischemic stroke¹²³. Accordingly, the European Association of Urology¹⁰ and the Endocrine Society⁹, both explicitly state testosterone replacement is contraindicated in eugonadal men and recommend frequent blood tests for hypogonadal patients receiving testosterone therapy.

Unfortunately, laypeople may subconsciously associate testosterone replacement therapy administered by a licensed physician with the stories of professional athletes who have been busted for using performance enhancing drugs in order to run faster, jump higher, and hit harder. The latter has drawn an astronomical amount of attention in the media, especially over the past decade. Journalists are piggybacking off of the success of these stories by irresponsibly

and inappropriately blurring the lines between a legitimate medical treatment and performance enhancing drug abuse.

Many in the general public hold a preconceived opinion of testosterone tarnished by the portrayal of violent, muscle-bound men with “roid-rage” in popular culture. For many years, the media has been catering to and perpetuating this prejudice. Of particular note is Chris Benoit, a well-known World Wrestling Entertainment athlete and abuser of anabolic-androgenic steroids who committed suicide in 2007 after murdering his wife and seven-year-old son. A slurry of media accounts proposed steroid as an explanation for his actions^{124,125}, prompting a federal investigation into performance enhancing drug use in professional wrestling.

Sex

Sex sells. It is not just an age-old adage, it is a verifiable scientific phenomena: provocative advertisements elicit physiological and cognitive reactions¹²⁶. The urge for reproduction is what has driven our evolution from single-celled organisms to sentient, powerful human beings. We, as a species, have a deeply rooted predisposition to respond to sexual imagery.

Testosterone is unequivocally associated to sex, and the media jumps at every opportunity to exploit the relationship. Two of the symptoms that most profoundly impact quality of life for hypogonadal males are erectile dysfunction and loss of libido.

The ability of a male to achieve an erection is contingent on parasympathetic innervation originating from S2-4 and the target vasculature. When aroused by tactile, auditory, or visual stimuli, the brain responds by activating the parasympathetic nervous system, which in turn excites the post-ganglionic cavernosal nerve. Downstream signaling leads to relaxation of the cavernosal smooth muscle and opening of the vascular space, thereby increasing arterial blood flow to the penis while venous outflow remains constant. As the corpora cavernosa fills with blood, the erectile tissues apply pressure against the tunica albuginae, occluding emissary veins and increasing penile rigidity.

As reviewed by Traish and Galoosian¹²⁷, there is evidence that testosterone plays an important role in several aspects of erectile physiology, including the function of trabecular smooth muscle, cavernosal and dorsal nerves, and vascular endothelium. Given the profound involvement of androgens in the erectile pathway, it is not surprising that the medical literature is teeming with studies correlating male sexual dysfunction with hypogonadism. In a cohort of 3,369 European men, erectile dysfunction was shown to be significantly related to decreased testosterone levels²³. Accordingly, testosterone therapy has been shown to improve sexual function in hypogonadal men¹²⁸⁻¹³².

The physiology of sexual desire, though less well understood than that of erections, is also highly dependent on testosterone. Several studies have identified the neurotransmitter dopamine as the key player in libido¹³³.

Androgens are known to activate nitric oxide pathways that facilitate dopamine release, thereby positively modulating sexual desire. Moreover, testosterone therapy has been shown to be extremely effective in increasing sexual desire in men¹³⁴.

Journalists know all too well that a sensational, hysteria-inducing headline will get people reading and a strong sexual component will keep them reading. Given the inextricable connection between androgens and all facets of male sexuality, it is no surprise that testosterone therapy has become such a hot topic in the mainstream media.

Hypermasculinity

The general public has an appetite for macabre. Evidence of this phenomenon abounds, from the box office earnings of violent action movies to the popularity of television shows glorifying serial killers and other types of deranged criminals. Aggression is interesting, and a common misconception exists that it is caused by testosterone. This inaccurate association is likely rooted in the belief that men are more aggressive than women [cite-Archer], and men also have higher levels of testosterone coursing through their bodies. “Roid-rage” has penetrated our society’s vernacular as a way to describe angry outbursts in men abusing anabolic-androgenic steroids, but the term’s recognition does not reflect its integrity when subjected to repeated scientific scrutiny. A recent well-designed study confirmed that administration of the same 600mg/wk dose of testosterone to men age 19-40 without preexisting

psychopathology did not increase aggressive behavior¹³⁵. Additionally, in 2000 a Harvard group found that just 16% of men receiving 600mg of testosterone per week, a markedly supraphysiological dose, experienced some degree of hypomania¹³⁶. While 16% is a significant portion of the sample population, it is important to distinguish the abuse of supraphysiological levels of anabolic steroids from testosterone therapy, a legitimate medical treatment for a medical disorder.

Recently, a Japanese group examined the effects of testosterone therapy in adult male patients with Prader-Willi syndrome (PWS), a rare genetic disorder known to cause hypogonadism, delayed and incomplete sexual development, short stature, behavioral issues, cognitive defects, obesity, and low muscle tone¹³⁷. The researchers observed tremendously beneficial outcomes, reporting a significant increase in secondary sex characteristics, bone density, and muscle mass, along with a decrease in body fat. Importantly, aggression, as measured on the Modified Overt Aggression Scale (MOAS) actually decreased during testosterone therapy, though the change was not significant (see figure 4). Moreover, there is evidence that low testosterone levels can contribute to mild depressive disorders, such as dysthymia¹³⁸.

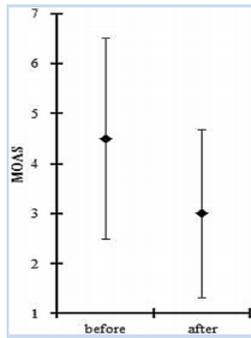


Figure 6. Changes in aggression in Prader-Willi Syndrome patients receiving testosterone therapy [Taken from Kido et al¹³⁷]. The graph shows that aggression, measured on the MOAS scale, decreased in PWS patients after the initiation of testosterone treatment.

As demonstrated, there is an abundance of evidence that therapeutic levels of testosterone do not cause an increase in aggression, and a lack of consistent evidence that abuse of supraphysiological androgen levels cause aggressive behavior. Despite the convincing science, mainstream media journalists continue to associate testosterone therapy with steroid abuse and imply that both cause an increase in aggressive behavior. In a 2014 article titled “In Men’s Fight Against Aging, How Much Risk to Take?” published in *The Wall Street Journal*, the author states, “Safety concerns have dogged testosterone products for decades. Large doses, which some bodybuilders take to bulk up, have been linked to aggression.”¹³⁹ Insulin, a drug used to treat diabetes mellitus, has a great deal in common with testosterone: they both are hormones produced naturally by the human body, synthetically synthesized to treat their respective deficiency disorders, and abused by bodybuilders and athletes in order to build muscle mass¹⁴⁰. Insulin misuse has the potential to be extremely lethal, yet the media seldom mentions it, and certainly does not cite it as an argument against its application as a therapy for patients with diabetes mellitus. To report that testosterone therapy is dangerous because a small subset of

people who abuse the substance become more aggressive is ignorant and unethical.

Anti-pharma

Many Americans harbor distrust for large corporations; indeed, politicians and journalists alike have made careers out of demonizing big business. This wariness has carried over to the lay public's view of large pharmaceutical companies (Big Pharma), and with good reason: the industry's history is burdened with fraud, data suppression, and questionable ethics¹⁴¹. Journalist willing to take on Big Pharma and 'stick it to the man' are extolled as white knights. Readers feel empowered when they believe someone is standing up for them, and the media harnesses this sense of solidarity to increase circulation.

CONCLUSION

Although it cannot be said with certainty until large, prospective, randomized controlled studies are conducted, the overwhelming majority of the evidence currently suggests that testosterone therapy is not associated with adverse cardiovascular outcomes⁴³⁻⁴⁵. If any correlation does exist, it is likely one that offers cardiovascular benefits to hypogonadal patients. At the present time, there is sufficient evidence for practitioners to recognize hypogonadism as a risk factor for mortality, atherosclerosis, and obesity³⁰⁻⁴⁰.

Interested parties eagerly await the results of the Testosterone Trials¹⁴², a coordinated set of seven clinical trials intended to definitively discern whether or not testosterone therapy in hypogonadal elderly men is efficacious in improving mobility, sexual function, fatigue, cognitive function, hemoglobin, bone density, and coronary artery plaque volume. Although this study is not primarily designed to examine the relationship between testosterone therapy and cardiovascular risk, it should provide valuable data to steer the conversation and future research.

The mainstream media has chosen to ignore the science suggesting testosterone therapy is safe and efficacious, and instead bring four flawed studies linking testosterone to cardiovascular risk into the public spotlight with sensationalist headlines and imbalanced reporting. This coverage has had a significant impact on the lay public's perception of testosterone therapy, and has even penetrated as far as to alter the discourse within the medical community.

Indeed, a geriatrician recently indicated that anyone who recognizes age-related hypogonadism as a legitimate and treatable medical condition is guilty of “disease mongering”¹⁴³.

The media plays an important role in healthcare, often serving as a valuable source of information for patients. This creates a level of transparency in the healthcare industry and holds pharmaceutical companies, researchers, and clinicians accountable for unethical practices. However, a very important line has been crossed in the media’s coverage of testosterone therapy in men: physicians, influenced by media-driven hysteria and fear, are withholding testosterone treatment from patients who suffer from hypogonadism. These abandoned patients are forced to either live without treatment for their medical condition, or turn to “anti-aging” walk-in testosterone clinics for a lower and dangerous standard of care. As Dr. Morgentaler so eloquently wrote in 2014, “The current outrage over the use of T therapy, anchored by the flimsiest of evidence regarding CV risk, should be regarded as hormonophobia. However, the true outrage is that men whose health and quality of life have been impacted by a highly prevalent hormone deficiency may fail to receive treatment due to social forces and hysteria that are unrelated to medical science.”¹⁴⁴ It is absolutely unethical for the media to interfere in the patient-physician relationship when the best evidence clinicians have available points to testosterone being a safe and efficacious treatment for the majority of hypogonadal men. When it

comes to healthcare, journalists should be bound by the same principles of bioethics that physicians are taught to adhere to: first, do no harm.

LIST OF JOURNAL ABBREVIATIONS

Adv. Consum. Res	Advances in Consumer Research
Albany Law Rev.	Albany Law Review
Am. J. Epidemiol.	American Journal of Epidemiology
Am. J. Kidney Dis.	American Journal of Kidney Disease
Am. J. Med. Genet.	American Journal of Medical Genetics
Am. J. Nephrol	American Journal of Nephrology
Am. J. Public Health	American Journal of Public Health
Arch. Anat. Histol. Embryol. Norm. Expérimentales	Archives d'anatomie, d'histologie et d'embryologie normales et expérimentales
Arch. Gen. Psychiatr.	Archives of General Psychiatry
Arch. Intern. Med.	Archives of Internal Medicine
Arthritis Rheum	Arthritis & Rheumatology
Biol. Reprod.	Biology of Reproduction
BJU Int.	BJU International
BMC Med	BMC Medicine
BMJ Case Rep	BMJ Case Reports
Br. J. Sports Med	British Journal of Sports Medicine
Cardiol. J.	Cardiology Journal
Clin. Endocrinol.	Clinical Endocrinology
Clin. Trials	Clinical Trials
Contemp. Clin. Trials	Contemporary Clinical Trials
Curr. Heart Fail. Rep	Current Heart Failure Reports

Curr. Opin. Endocrinol. Diabetes Obes.	Current Opinion in Endocrinology, Diabetes, and Obesity
Curr. Urol. Rep.	Current Urology Reports
Endocr. Rev.	Endocrine Reviews
Eur. J. Endocrinol.	European Journal of Endocrinology
Eur. Urol.	European Urology
Exp. Gerontol.	Experimental Gerontology
Heart Br. Card. Soc	Heart: British Cardiovascular Society
Hepatol.	Hepatology
Hypertens. Res.	Hypertension Research
Int. J. Cardiol.	International Journal of Cardiology
Int. J. Clin. Pract.	International Journal of Clinical Practice
Int. J. Impot. Res.	International Journal of Impotence Research
Int. J. Sports Med	International Journal of Sports Medicine
JAMA	JAMA: The Journal of the American Medical Association
J. Am. Gastroenterol. Assoc	Journal of the American Gastroenterology Association
J. Am. Soc. Clin. Oncol	Journal of the American Society of Clinical Oncology
J. Am. Soc. Health-Syst. Pharm.	Journal of the American Society of Health- System Pharmacy Society
J. Clin. Endocrinol. Metab.	Journal of Clinical Endocrinology and Metabolism
J. Clin. Epidemiol.	Journal of Clinical Epidemiology
J. Clin. Gastroenterol.	Journal of Clinical Gastroenterology

J. Clin. Invest	Journal of Clinical Investigation
J. Pharm. Pract.	Journal of Pharmaceutical Practice
J. Psychiatr. Res	Journal of Psychiatric Research
J. Sex. Med.	Journal of Sexual Medicine
J. Urol.	Journal of Urology
Korean J. Urol.	Korean Journal of Urology
Mayo Clin. Proc.	Mayo Clinic Proceedings
Med. Care	Medical Care
N. Engl. J. Med.	New England Journal of Medicine
Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc	Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association
Obes.	Obesity
Ther. Clin. Risk Manag	Therapeutics and Clinical Risk Management
Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res.	Value in Health: The Journal of the International Society Pharmacoeconomics and Outcomes Research
Wien. Med. Wochenschr	Wiener Medizinische Wochenschrift
World J. Biol. Psychiatry	World Journal of Biological Psychiatry
World J. Mens Health	World Journal of Mens Health
World J. Urol.	World Journal of Urology

REFERENCES

1. Klein, M. [Berthold's article: Transplantation of the testes (1849)]. *Arch. Anat. Histol. Embryol. Norm. Expérimentales* **51**, 379–386 (1968).
2. FREEMAN, E. R., BLOOM, D. A. & McGUIRE, E. J. A BRIEF HISTORY OF TESTOSTERONE. *J. Urol.* **165**, 371–373 (2001).
3. Kochakian, C. D. History, chemistry and pharmacodynamics of anabolic-androgenic steroids. *Wien. Med. Wochenschr.* 1946 **143**, 359–363 (1993).
4. Über krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder aus Cholesterin bereitetes Androsteron. : Hoppe-Seyler's Zeitschrift für physiologische Chemie. at <<http://www.degruyter.com/view/j/bchm2.1935.233.issue-5-6/bchm2.1935.233.5-6.281/bchm2.1935.233.5-6.281.xml>>
5. Aub, J. C. Endocrines: The Use of Testosterone. *N. Engl. J. Med.* **222**, 877–881 (1940).
6. Aub, J. C. & Kety, S. S. Recent Advances in Testosterone Therapy. *N. Engl. J. Med.* **228**, 338–343 (1943).
7. Lesser, M. A. The Treatment of Angina Pectoris with Testosterone Propionate. *N. Engl. J. Med.* **228**, 185–188 (1943).
8. American Urological Association. An Important Announcement from the AUA. (2014). at <<https://www.auanet.org/common/pdf/advocacy/advocacy-by-topic/Testosterone-FDA.pdf>>
9. Bhasin, S. *et al.* Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. **95**, 2536–2559 (2010).
10. Dohle, G. R. *et al.* European Association of Urology Guidelines on Male Hypogonadism. (2012). at <http://www.uroweb.org/gls/pdf/16_Male_Hypogonadism_LR%20II.pdf>
11. Guay, A., Seftel, A. D. & Traish, A. Hypogonadism in men with erectile dysfunction may be related to a host of chronic illnesses. *Int. J. Impot. Res.* **22**, 9–19 (2010).
12. Hollander, N. & Hollander, V. P. The microdetermination of testosterone in human spermatic vein blood. *J. Clin. Endocrinol. Metab.* **18**, 966–971 (1958).

13. Vermeulen, A., Rubens, R. & Verdonck, L. Testosterone secretion and metabolism in male senescence. *J. Clin. Endocrinol. Metab.* **34**, 730–735 (1972).
14. Giusti, G. *et al.* Age-related secretion of androstenedione, testosterone and dihydrotestosterone by the human testis. *Exp. Gerontol.* **10**, 241–245 (1975).
15. Bremner, W. J., Vitiello, M. V. & Prinz, P. N. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J. Clin. Endocrinol. Metab.* **56**, 1278–1281 (1983).
16. Tenover, J. S., Matsumoto, A. M., Plymate, S. R. & Bremner, W. J. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. *J. Clin. Endocrinol. Metab.* **65**, 1118–1126 (1987).
17. Gray, A., Berlin, J. A., McKinlay, J. B. & Longcope, C. An examination of research design effects on the association of testosterone and male aging: results of a meta-analysis. *J. Clin. Epidemiol.* **44**, 671–684 (1991).
18. Ferrini, R. L. & Barrett-Connor, E. Sex hormones and age: a cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. *Am. J. Epidemiol.* **147**, 750–754 (1998).
19. Zmuda, J. M. *et al.* Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. *Am. J. Epidemiol.* **146**, 609–617 (1997).
20. Morley, J. E. *et al.* Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism.* **46**, 410–413 (1997).
21. Feldman, H. A. *et al.* Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J. Clin. Endocrinol. Metab.* **87**, 589–598 (2002).
22. Kaufman, J. M. & Vermeulen, A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr. Rev.* **26**, 833–876 (2005).
23. Wu, F. C. W. *et al.* Identification of Late-Onset Hypogonadism in Middle-Aged and Elderly Men. *N. Engl. J. Med.* **363**, 123–135 (2010).
24. Harman, S. M. *et al.* Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J. Clin. Endocrinol. Metab.* **86**, 724–731 (2001).

25. Neaves, W. B., Johnson, L., Porter, J. C., Parker, C. R. & Petty, C. S. Leydig cell numbers, daily sperm production, and serum gonadotropin levels in aging men. *J. Clin. Endocrinol. Metab.* **59**, 756–763 (1984).
26. Mahmoud, A. M. *et al.* Testicular volume in relation to hormonal indices of gonadal function in community-dwelling elderly men. *J. Clin. Endocrinol. Metab.* **88**, 179–184 (2003).
27. Zirkin, B. R. & Chen, H. Regulation of Leydig cell steroidogenic function during aging. *Biol. Reprod.* **63**, 977–981 (2000).
28. Kaufman, J. M., Giri, M., Deslypere, J. M., Thomas, G. & Vermeulen, A. Influence of age on the responsiveness of the gonadotrophs to luteinizing hormone-releasing hormone in males. *J. Clin. Endocrinol. Metab.* **72**, 1255–1260 (1991).
29. Veldhuis, J. D., Urban, R. J., Lizarralde, G., Johnson, M. L. & Iranmanesh, A. Attenuation of luteinizing hormone secretory burst amplitude as a proximate basis for the hypoandrogenism of healthy aging in men. *J. Clin. Endocrinol. Metab.* **75**, 707–713 (1992).
30. Shores, M. M., Matsumoto, A. M., Sloan, K. L. & Kivlahan, D. R. Low serum testosterone and mortality in male veterans. *Arch. Intern. Med.* **166**, 1660–1665 (2006).
31. Malkin, C. J. *et al.* Low serum testosterone and increased mortality in men with coronary heart disease. *Heart Br. Card. Soc.* **96**, 1821–1825 (2010).
32. Pye, S. R. *et al.* Late-onset hypogonadism and mortality in aging men. *J. Clin. Endocrinol. Metab.* **99**, 1357–1366 (2014).
33. Muraleedharan, V., Marsh, H., Kapoor, D., Channer, K. S. & Jones, T. H. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur. J. Endocrinol. Eur. Fed. Endocr. Soc.* **169**, 725–733 (2013).
34. Laughlin, G. A., Barrett-Connor, E. & Bergstrom, J. Low serum testosterone and mortality in older men. *J. Clin. Endocrinol. Metab.* **93**, 68–75 (2008).
35. Khaw, K.-T. *et al.* Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* **116**, 2694–2701 (2007).

36. Haring, R. *et al.* Low serum testosterone is associated with increased mortality in men with stage 3 or greater nephropathy. *Am. J. Nephrol.* **33**, 209–217 (2011).
37. Corona, G. *et al.* Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. *J. Sex. Med.* **7**, 1557–1564 (2010).
38. Vikan, T., Schirmer, H., Njølstad, I. & Svartberg, J. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromsø Study. *Eur. J. Endocrinol. Eur. Fed. Endocr. Soc.* **161**, 435–442 (2009).
39. Yeap, B. B. *et al.* In older men, higher plasma testosterone or dihydrotestosterone is an independent predictor for reduced incidence of stroke but not myocardial infarction. *J. Clin. Endocrinol. Metab.* **99**, 4565–4573 (2014).
40. Traish, A. M. Adverse health effects of testosterone deficiency (TD) in men. *Steroids* **88**, 106–116 (2014).
41. Akishita, M. *et al.* Low Testosterone Level Is an Independent Determinant of Endothelial Dysfunction in Men. *Hypertens. Res.* **30**, 1029–1034 (2007).
42. Svartberg, J. *et al.* Association of endogenous testosterone with blood pressure and left ventricular mass in men. The Tromsø Study. *Eur. J. Endocrinol.* **150**, 65–71 (2004).
43. Baillargeon, J. *et al.* Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. *Ann. Pharmacother.* **48**, 1138–1144 (2014).
44. Etminan, M., Skeldon, S. C., Goldenberg, S. L., Carleton, B. & Brophy, J. M. Testosterone therapy and risk of myocardial infarction: a pharmacoepidemiologic study. *Pharmacotherapy* **35**, 72–78 (2015).
45. Tan, R. S., Cook, K. R. & Reilly, W. G. Myocardial Infarction and Stroke Risk in Young Healthy Men Treated with Injectable Testosterone. *Int. J. Endocrinol.* at <<http://www.hindawi.com/journals/ije/2015/970750/abs/>>
46. Basaria, S. *et al.* Adverse events associated with testosterone administration. *N. Engl. J. Med.* **363**, 109–122 (2010).
47. Xu, L., Freeman, G., Cowling, B. J. & Schooling, C. M. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med.* **11**, 108 (2013).

48. Vigen, R. *et al.* Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* **310**, 1829–1836 (2013).
49. Finkle, W. D. *et al.* Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PloS One* **9**, e85805 (2014).
50. Wolfe, S. & Carome, M. Petition to the FDA for Black Box Warnings on all Testosterone Products. (2014). at <<http://www.citizen.org/documents/2184.pdf>>
51. Woodcock. *Citizen petition denial response from FDA CDER to Public Citizen*. (Food and Drug Administration, 2014). at <http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Petition.pdf>
52. Araujo, A. B. *et al.* Sex steroids and all-cause and cause-specific mortality in men. *Arch. Intern. Med.* **167**, 1252–1260 (2007).
53. Carrero, J. J. *et al.* Low serum testosterone increases mortality risk among male dialysis patients. *J. Am. Soc. Nephrol. JASN* **20**, 613–620 (2009).
54. Tivesten, A. *et al.* Low serum testosterone and estradiol predict mortality in elderly men. *J. Clin. Endocrinol. Metab.* **94**, 2482–2488 (2009).
55. Militaru, C., Donoiu, I., Dracea, O. & Ionescu, D.-D. Serum testosterone and short-term mortality in men with acute myocardial infarction. *Cardiol. J.* **17**, 249–253 (2010).
56. Ponikowska, B. *et al.* Gonadal and adrenal androgen deficiencies as independent predictors of increased cardiovascular mortality in men with type II diabetes mellitus and stable coronary artery disease. *Int. J. Cardiol.* **143**, 343–348 (2010).
57. Menke, A. *et al.* Sex steroid hormone concentrations and risk of death in US men. *Am. J. Epidemiol.* **171**, 583–592 (2010).
58. Haring, R. *et al.* Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. *Eur. Heart J.* **31**, 1494–1501 (2010).
59. Carrero, J. J. *et al.* Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc.* **26**, 184–190 (2011).

60. Kyriazis, J. *et al.* Low serum testosterone, arterial stiffness and mortality in male haemodialysis patients. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc.* **26**, 2971–2977 (2011).
61. Hyde, Z. *et al.* Low free testosterone predicts mortality from cardiovascular disease but not other causes: the Health in Men Study. *J. Clin. Endocrinol. Metab.* **97**, 179–189 (2012).
62. Lerchbaum, E. *et al.* Combination of low free testosterone and low vitamin D predicts mortality in older men referred for coronary angiography. *Clin. Endocrinol. (Oxf.)* **77**, 475–483 (2012).
63. Haring, R. *et al.* Association of sex steroids, gonadotrophins, and their trajectories with clinical cardiovascular disease and all-cause mortality in elderly men from the Framingham Heart Study. *Clin. Endocrinol. (Oxf.)* **78**, 629–634 (2013).
64. D’Andrea, A. *et al.* Left ventricular early myocardial dysfunction after chronic misuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis. *Br. J. Sports Med.* **41**, 149–155 (2007).
65. Karila, T. a. M., Karjalainen, J. E., Mäntysaari, M. J., Viitasalo, M. T. & Seppälä, T. A. Anabolic androgenic steroids produce dose-dependant increase in left ventricular mass in power athletes, and this effect is potentiated by concomitant use of growth hormone. *Int. J. Sports Med.* **24**, 337–343 (2003).
66. LeBrasseur, N. K. *et al.* Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (The TOM Trial): design and methods. *Contemp. Clin. Trials* **30**, 133–140 (2009).
67. Morgentaler, A. *et al.* Testosterone Therapy and Cardiovascular Risk: Advances and Controversies. *Mayo Clin. Proc.* **90**, 224–251 (2015).
68. Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. The Copenhagen Study Group for Liver Diseases. *Hepatol. Baltim. Md* **6**, 807–813 (1986).
69. Xu, S. *et al.* Extension of Kaplan-Meier methods in observational studies with time-varying treatment. *Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res.* **15**, 167–174 (2012).
70. Correction: Incorrect language. *JAMA* **311**, 306–306 (2014).
71. Traish, A. M., Guay, A. T. & Morgentaler, A. Death by testosterone? We think not! *J. Sex. Med.* **11**, 624–629 (2014).

72. Lee, W. C. *et al.* Relationship between Serum Testosterone and Cardiovascular Disease Risk Determined Using the Framingham Risk Score in Male Patients with Sexual Dysfunction. *World J. Mens Health* **32**, 139–144 (2014).
73. Dupree, J. M., Ramasamy, R., Kovac, J. R., Langille, G. & Lipshultz, L. I. Re: Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *Eur. Urol.* **66**, 175–176 (2014).
74. Kass, D. A. Cardiac role of cyclic-GMP hydrolyzing phosphodiesterase type 5: from experimental models to clinical trials. *Curr. Heart Fail. Rep.* **9**, 192–199 (2012).
75. Takimoto, E. *et al.* Regulator of G protein signaling 2 mediates cardiac compensation to pressure overload and antihypertrophic effects of PDE5 inhibition in mice. *J. Clin. Invest.* **119**, 408–420 (2009).
76. Giannetta, E. *et al.* Is chronic inhibition of phosphodiesterase type 5 cardioprotective and safe? A meta-analysis of randomized controlled trials. *BMC Med.* **12**, 185 (2014).
77. Quick Study: Testosterone supplement may have cardiovascular risks for older men. *The Washington Post* (2010). at <<http://www.washingtonpost.com/wp-dyn/content/article/2010/07/12/AR2010071204179.html>>
78. Testosterone treatments linked to heart risks. *USA TODAY* at <<http://www.usatoday.com/story/news/nation/2013/11/05/testosterone-heart-attacks/3448543/>>
79. The Editorial Board. Overselling Testosterone, Dangerously. *The New York Times* (2014). at <<http://www.nytimes.com/2014/02/05/opinion/overselling-testosterone-dangerously.html>>
80. Kahn, H. A. *et al.* The Framingham Eye Study. I. Outline and major prevalence findings. *Am. J. Epidemiol.* **106**, 17–32 (1977).
81. Vaitkevicius, P. V. *et al.* Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* **88**, 1456–1462 (1993).
82. Gunasekaran, U. & Gannon, M. Type 2 diabetes and the aging pancreatic beta cell. *Aging* **3**, 565–575 (2011).
83. *NIDCD Fact Sheet: Age-Related Hearing Loss*. (October 21014). at <<http://www.nidcd.nih.gov/staticresources/health/hearing/NIDCD-Age-Related-Hearing-Loss.pdf>>

84. Olson, R. E. Prevention and control of chronic disease. I. Cardiovascular disease--with particular attention to atherosclerosis. *Am. J. Public Health Nations Health* **49**, 1120–1128 (1959).
85. Maclaughlin, E. J., Sleeper, R. B., McNatty, D. & Raehl, C. L. Management of age-related osteoporosis and prevention of associated fractures. *Ther. Clin. Risk Manag.* **2**, 281–295 (2006).
86. Rasch, E. K., Hirsch, R., Paulose-Ram, R. & Hochberg, M. C. Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: effect of different methods of case classification. *Arthritis Rheum.* **48**, 917–926 (2003).
87. Lee, J. *et al.* Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* **5**, 1392–1398 (2007).
88. McGrother, C. *et al.* Epidemiology and etiology of urinary incontinence in the elderly. *World J. Urol.* **16 Suppl 1**, S3–9 (1998).
89. Puma, J. L. Don't Ask Your Doctor About 'Low T'. *The New York Times* (2014). at <<http://www.nytimes.com/2014/02/04/opinion/dont-ask-your-doctor-about-low-t.html>>
90. Saad, F., Haider, A., Doros, G. & Traish, A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obes. Silver Spring Md* **21**, 1975–1981 (2013).
91. Traish, A. M. Testosterone and weight loss: the evidence. *Curr. Opin. Endocrinol. Diabetes Obes.* **21**, 313–322 (2014).
92. Men's Use of Testosterone on the Rise. *Well* at <<http://well.blogs.nytimes.com/2013/06/03/mens-use-of-hormone-on-the-rise/>>
93. Baillargeon, J., Urban, R. J., Ottenbacher, K. J., Pierson, K. S. & Goodwin, J. S. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern. Med.* **173**, 1465–1466 (2013).
94. Resko, J. A. & Eik-nes, K. B. Diurnal testosterone levels in peripheral plasma of human male subjects. *J. Clin. Endocrinol. Metab.* **26**, 573–576 (1966).
95. Singer, N. Selling That New-Man Feeling. *The New York Times* (2013). at <<http://www.nytimes.com/2013/11/24/business/selling-that-new-man-feeling.html>>

96. Mohamoud, M. A. Testosterone Replacement Therapy (TRT) Drug Utilization Patterns. (2014). at <<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM416461.pdf>>
97. Aitken, M., Kleinrock, M., Lyle, J. & Caskey. *Medicine use and shifting costs of healthcare: A review of the use of medicines in the United States in 2013*. (IMS Institute for Healthcare Informatics, 2014). at <http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Reports/Secure/IIHI_US_Use_of_Meds_for_2013.pdf>
98. *Health, United States, 2013: With Special Feature on Prescription Drugs*. (National Center for Health Statistics, 2014).
99. Schumock, G. T. *et al*. National trends in prescription drug expenditures and projections for 2014. *Am. J. Health-Syst. Pharm. AJHP Off. J. Am. Soc. Health-Syst. Pharm.* **71**, 482–499 (2014).
100. Ayala, E. S., Meuret, A. E. & Ritz, T. Treatments for blood-injury-injection phobia: a critical review of current evidence. *J. Psychiatr. Res.* **43**, 1235–1242 (2009).
101. Aikin, K. J., Swasy, J. L. & Braman. *Patient and Physician Attitudes and Behaviors Associated With DTC Promotion of Prescription Drugs - Summary of FDA Survey Research Results*. (U.S. Department of Health and Human Services Food and Drug Administration, 2004). at <<http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/DrugMarketingAdvertisingandCommunicationsResearch/UCM152890.pdf>>
102. Weissman, J. S. *et al*. Consumers' reports on the health effects of direct-to-consumer drug advertising. *Health Aff. Proj. Hope* **Suppl Web Exclusives**, W3–82–95 (2003).
103. Kuehn, B. M. FDA weighs limits for online ads. *JAMA* **303**, 311–313 (2010).
104. Donohue, J. M., Berndt, E. R., Rosenthal, M., Epstein, A. M. & Frank, R. G. Effects of pharmaceutical promotion on adherence to the treatment guidelines for depression. *Med. Care* **42**, 1176–1185 (2004).
105. Connors, A. L. Big bad pharma: an ethical analysis of physician-directed and consumer-directed marketing tactics. *Albany Law Rev.* **73**, 243–282 (2009).

106. Abel, G. A., Lee, S. J. & Weeks, J. C. Direct-to-consumer advertising in oncology: a content analysis of print media. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **25**, 1267–1271 (2007).
107. Ventola, C. L. Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic? *P T Peer-Rev. J. Formul. Manag.* **36**, 669–684 (2011).
108. *United States Food and Drug Administration (FDA) Pediatric Advisory Committee: AndroGel® (testosterone gel) 1% CIII Briefing Book.* (Solvay Pharmaceuticals, Inc., 2009).
109. Mulligan, T., Frick, M. F., Zuraw, Q. C., Stemhagen, A. & McWhirter, C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int. J. Clin. Pract.* **60**, 762–769 (2006).
110. *Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients.* (2013). at <<http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients>>
111. *Eli Lilly's advertising spending on Cymbalta in the United States in 2011 and 2012 (in million U.S. dollars).* at <<http://www.statista.com/statistics/318298/cymbalta-ad-spend-usa/>>
112. *2012 U.S. Pharmaceutical Promotion Spending.* (Cegedim Strategic Data). at <http://www.skainfo.com/health_care_market_reports/2012_promotional_spending.pdf>
113. *Top 20 companies by DTC spending, 2012.* (Medical Marketing & Media). at <http://media.mmm-online.com/documents/44/top_20_dtc_charts_10971.pdf>
114. 9, A. & 2012. Top 10 Drug Advertising Spends -- Q1 2012. *FiercePharma* at <<http://www.fiercepharma.com/special-reports/top-10-drug-advertising-spends-q1-2012>>
115. Ackermann, S. *et al.* Testosterone levels in healthy men are related to amygdala reactivity and memory performance. *Psychoneuroendocrinology* **37**, 1417–1424 (2012).
116. Kennelly, M. F. *Testosterone Replacement Therapy Products Liability Litigation Coordinated Pretrial Proceedings.* at <http://www.gpo.gov/fdsys/pkg/USCOURTS-ilnd-1_14-cv-01748/pdf/USCOURTS-ilnd-1_14-cv-01748-2.pdf>

117. Silverman, E. Doctors try to influence a medical journal poll on testosterone treatments. (2014). at <<http://blogs.wsj.com/pharmalot/2014/12/02/doctors-try-to-influence-a-medical-journal-poll-on-testosterone-treatments/>>
118. Testosterone-Replacement Therapy. *N. Engl. J. Med.* **371**, 2032–2034 (2014).
119. Wallis, C. J. D., Brotherhood, H. & Pommerville, P. J. Testosterone deficiency syndrome and cardiovascular health: An assessment of beliefs, knowledge and practice patterns of general practitioners and cardiologists in Victoria, BC. *Can. Urol. Assoc. J. J. Assoc. Urol. Can.* **8**, 30–33 (2014).
120. Storer, T. W. *et al.* Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *J. Clin. Endocrinol. Metab.* **88**, 1478–1485 (2003).
121. Stimac, D., Milić, S., Dintinjana, R. D., Kovac, D. & Ristić, S. Androgenic/Anabolic steroid-induced toxic hepatitis. *J. Clin. Gastroenterol.* **35**, 350–352 (2002).
122. Luciano, R. L., Castano, E., Moeckel, G. & Perazella, M. A. Bile acid nephropathy in a bodybuilder abusing an anabolic androgenic steroid. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **64**, 473–476 (2014).
123. Shamloul, R. M., Aborayah, A. F., Hashad, A. & Abd-Allah, F. Anabolic steroids abuse-induced cardiomyopathy and ischaemic stroke in a young male patient. *BMJ Case Rep.* **2014**, (2014).
124. Goodman, B. Wrestler Killed Wife and Son, Then Himself. *The New York Times* (2007). at <<http://www.nytimes.com/2007/06/27/us/27wrestler.html>>
125. O’connor, A. Wrestler Found to Have Taken Testosterone. *The New York Times* (2007). at <<http://www.nytimes.com/2007/07/18/us/18wrestler.html>>
126. Belch, M. A., Holgerson, B. E., Belch, G. E. & Koppman, J. Psychophysiological and Cognitive Responses to Sex in Advertising. *Adv. Consum. Res.* **9**, 424–427 (1982).
127. Traish, A. M. & Galoosian, A. Androgens modulate endothelial function and endothelial progenitor cells in erectile physiology. *Korean J. Urol.* **54**, 721–731 (2013).
128. Jacob, B. C. Testosterone replacement therapy in males with erectile dysfunction. *J. Pharm. Pract.* **24**, 298–306 (2011).

129. Morales, A. Androgens are fundamental in the maintenance of male sexual health. *Curr. Urol. Rep.* **12**, 453–460 (2011).
130. Traish, A. M., Goldstein, I. & Kim, N. N. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. *Eur. Urol.* **52**, 54–70 (2007).
131. Saad, F. *et al.* Effects of testosterone on erectile function: implications for the therapy of erectile dysfunction. *BJU Int.* **99**, 988–992 (2007).
132. Boloña, E. R. *et al.* Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin. Proc.* **82**, 20–28 (2007).
133. Pfaus, J. G. in *Cancer and Sexual Health* (eds. Mulhall, J. P., Incrocci, L., Goldstein, I. & Rosen, R.) 25–33 (Humana Press, 2011). at <http://link.springer.com/chapter/10.1007/978-1-60761-916-1_3>
134. Allan, C. A., Forbes, E. A., Strauss, B. J. G. & McLachlan, R. I. Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. *Int. J. Impot. Res.* **20**, 396–401 (2008).
135. Tricker, R. *et al.* The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men—a clinical research center study. *J. Clin. Endocrinol. Metab.* **81**, 3754–3758 (1996).
136. Pope, H. G., Kouri, E. M. & Hudson, J. I. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. *Arch. Gen. Psychiatry* **57**, 133–140; discussion 155–156 (2000).
137. Kido, Y. *et al.* Testosterone replacement therapy to improve secondary sexual characteristics and body composition without adverse behavioral problems in adult male patients with Prader-Willi syndrome: an observational study. *Am. J. Med. Genet. A.* **161A**, 2167–2173 (2013).
138. Seidman, S. N. Testosterone deficiency and mood in aging men: pathogenic and therapeutic interactions. *World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry* **4**, 14–20 (2003).
139. Beck, M. In Men’s Fight Against Aging, How Much Risk to Take? *Wall Street Journal* (2014). at <<http://www.wsj.com/articles/in-mens-fight-against-aging-how-much-risk-to-take-1414443065>>
140. Evans, P. J. & Lynch, R. M. Insulin as a drug of abuse in body building. *Br. J. Sports Med.* **37**, 356–357 (2003).

141. Gøtzsche, P. C. Big pharma often commits corporate crime, and this must be stopped. *BMJ* **345**, e8462 (2012).
142. Snyder, P. J. *et al.* The Testosterone Trials: Seven coordinated trials of testosterone treatment in elderly men. *Clin. Trials Lond. Engl.* **11**, 362–375 (2014).
143. Perls, T. & Handelsman, D. J. Disease Mongering of Age-Associated Declines in Testosterone and Growth Hormone Levels. *J. Am. Geriatr. Soc.* (2015). doi:10.1111/jgs.13391
144. Morgentaler, A. Testosterone, Cardiovascular Risk, and Hormonophobia. *J. Sex. Med.* **11**, 1362–1366 (2014).

CURRICULUM VITAE

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Education

Boston University – Division of Graduate Medical Sciences
Boston, MA

M.S. Medical Sciences

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The Ohio State University
Columbus, OH

B.S. Molecular Genetics

August 2012

Experience

Boston Medical Center
MA

Boston,

Otolaryngology Scribe

August 2014 –

Present

- Typed an accurate record of the physician-patient interaction into the Electronic Medical Record in real-time, allowing the physician to focus his attention on the patient.

The Ohio State University Wexner Medical Center
Columbus, OH

Research Assistant, Division of Nephrology

July 2012 – June

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- Worked in the lab of Brad Rovin MD
- Used proteomics and mRNA expression profiles to identify non-invasive biomarkers of Lupus Nephritis in the glomeruli of kidney biopsies collected using laser capture microdissection.

The Ohio State University Department of Molecular Genetics
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Columbus,

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- Individually worked with physicians to customize administrative documents used for patient charts.
- Identified endoreplication-specific genes by performing clonal analysis experiments in the salivary glands of *Drosophila melanogaster*.

Publications

Abstracts

- Vance, J.C., K.M. Ware, K. Qamri, L.A. Hebert, A.A. Satoskar, G. Nadasdy, I. Ivanov, T. Nadasdy, B.H. Rovin, and S.V. Brodsky: Oral warfarin increases blood pressure in control and 5/6 nephrectomy rats. *J. Am. Soc. Nephrol.*, Nov 2013.
- Parikh, S., A. Malvar, J.C. Vance, H. Song, B.J. Lococo, V.G. Alberton, and B.H. Rovin: Molecular characterization of renal responses in lupus nephritis using serial kidney biopsies. *J. Am. Soc. Nephrol.*, Nov 2013.

Peer Reviewed Papers

- Parikh, S.V., A. Malvar, H. Song, V. Alberton, B. Lococo, J. Vance, J. Zhang, L. Yu, B.H. Rovin: Molecular profiling of the kidney biopsy differentiates early treatment responders from non-responders in lupus nephritis. *J. Am. Soc. Nephrol* [Submitted for review Dec 2014]
- Ware, K.M., J.C. Vance, Z. Qamri, L.A. Hebert, A.A. Satoskar, G. Nadasay, I. Ivanov, T. Nadasay, B.H. Rovin, and S.V. Brodsky: Oral warfarin and thrombin inhibitor dabigatran increase blood pressure in rats: Hidden danger of anticoagulants. *Am J Hypertens.* 2014 Jul 13.