"FOREVER YOUNG" *

TESTOSTERONE REPLACEMENT THERAPY: A BLOCKBUSTER DRUG DESPITE FLABBY EVIDENCE AND BROKEN PROMISES

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* Bob Dylan. In Planet Waves, Asylum Records, US, 1974

Abstract

In the last decade testosterone replacement therapy (TRT) has been increasingly prescribed to treat a controversial condition known as 'late-onset hypogonadism (LOH)'. This syndrome is diagnosed in men who, for no discernible reason other than older age, obesity or ill health have serum testosterone concentrations below the normal range for healthy young men and report one or more of the following symptoms: muscle weakness or wasting, mood, behaviour and cognition related symptoms and sexual function or libido impairment. However, recent evidence has demonstrated that testosterone drugs do not substantially ameliorate these symptoms and, more worryingly, that their long-term use may be associated with severe adverse effects (i.e., increased risk of prostate cancer, stroke and myocardial infarction, worsening of benign prostatic hyperplasia symptoms, testicular atrophy). Nonetheless, testosterone drugs have exhibited extraordinary commercial success and their pharmaceutical sales are steadily rising. Behind this apparently unjustifiable trend there are deliberate, well designed direct and indirect pharmaceutical marketing initiatives that exploit the conviction rooted in contemporary society that testosterone can reverse the effects of ageing and ensure social accomplishment. Commercial mechanisms have laid the foundation for disease mongering of LOH and also have resulted a considerable expansion of the indications for treatment. This promotion model deserves particular attention since it is applicable to any drug with a purportedly favourable risk-benefit ratio not supported by evidence.

Key words: late onset hypogonadism, LOH, testosterone, testosterone replacement therapy, TRT, risk-benefit ratio, marketing campaign, disease mongering

Introduction

The Food and Drug Administration (FDA) approved testosterone as a replacement therapy only for men who have low testosterone levels attributable to disorders of the testicles, pituitary gland, or brain that cause hypogonadism (FDA Drug Safety Communication, 2015). However, in the last decade testosterone products are being increasingly prescribed to treat a controversial condition known as 'late-onset hypogonadism (LOH)'. This syndrome, also referred to as 'age related hypogonadism', is associated with advancing age and is characterized by a deficiency in serum testosterone levels (below the normal range for healthy young men) and by symptoms reminiscent of hypogonadism in young men, such as sexual dysfunction, muscle weakness, obesity, osteoporosis, hot flushes, insomnia, fatigue, poor concentration and depression (Wang *et al.*, 2009; Huhtaniemi and Forti, 2011; Huhtaniemi, 2014).

Late-onset hypogonadism may be caused by age-related primary testicular failure or, more commonly, by a hypothalamic-pituitary failure. However, the decline of testosterone observed in the latter scenario is very rarely a direct effect of biological ageing or the consequence of organic diseases of the hypothalamic-pituitary unit. Most often it is due to the chronic conditions (i.e. overweight/obesity, diabetes, hypertension, hepatic or renal failure, chronic obstructive lung disease, and inflammatory arthritis) associated with this form of LOH as well as to the medications to treat them (Huhtaniemi and Forti, 2011; Huhtaniemi, 2014).

Testosterone products used to treat LOH are commonly known as 'Low testosterone drugs' or, simply, as 'Low-T drugs'. Furthermore, since age-related testosterone decrease has been associated with an increase in atherosclerosis and cardiovascular risk, some authors speculated that replacing testosterone would reduce these risks (Kloner *et al.*, 2016).

Recently, Huo *et al.* published an interesting systematic review including 156 randomised controlled trials (RCT) that evaluated the use of testosterone drugs against a placebo or an inactive comparator in adult men for one or more 'Low-T' symptoms and for one or more cardiovascular

endpoints (i.e. ischemia/angina, congestive heart failure, lipids, inflammatory and coagulation markers) (Huo *et al*., 2016). They concluded that the prescription of testosterone supplementation did not show consistent benefits for cardiovascular risk, sexual function, mood and behaviour, or cognition and, despite an increase in muscle strength, it did not have beneficial effects on overall physical function (Huo *et al*., 2016). Moreover, of particular relevance here, is that the safety of testosterone consumption is doubtful. In fact it seems to be associated with adverse effects, such as an increased risk of prostate cancer, strokes and myocardial infarction, worsening symptoms of benign prostatic hyperplasia and testicular atrophy (FDA Drug Safety Communication, 2015; McCarthy, 2016). Accordingly, in a recent published safety communication, the FDA required labelling changes for all testosterone products to reflect the possible increased risks of heart attacks and strokes associated with testosterone use (FDA Drug Safety Communication, 2015). Furthermore, testosterone administration has been associated with development of acne, gynecomastia, peripheral edema, and polycythemia. Injections of testosterone undecanoate rarely have caused pulmonary oil microembolism and anaphylactic reactions (Safety of Testosterone Replacement Therapy, 2016).

The strength of the evidence in terms of both benefits and risks prompted Huo *et al*. to conclude that further trials on this issue are no longer necessary (Huo *et al.*, 2016). Nonetheless, this conclusion might be premature (Yeap, 2016). In fact, the initial results of the National Institutes of Health–sponsored Testosterone Trials showed a moderate benefit of testosterone supplementation with respect to sexual function in older men (Snyder *et al*., 2016; Orwoll, 2016). Furthermore, additional evidence has yet to be disclosed: results of four of the Testosterone Trials will soon be published and an Australian trial (T4DM, ACTRN12612000287831) testing the testosterone supplementation for the prevention of diabetes mellitus in overweight men with impaired glucose tolerance is currently ongoing (Snyder *et al*., 2016; Yeap, 2016). Finally, the supposed beneficial effect of testosterone supplementation on the risk of stroke and of all-cause mortality is waiting to

be tested with adequately powered randomised controlled trials (Yeap *et al*., 2014a; Yeap *et al*., 2014b; Yeap *et al*., 2016).

Despite the uncertainties about both the benefits and the safety profile of testosterone replacement therapy, U.S. pharmaceutical sales of testosterone increased from $324 million in 2002 to $2 billion in 2012 and, surprisingly, are continuing to grow in dozens of countries (Perls and Handelsman, 2015; Huo *et al.,* 2016). In fact, according to Global Industry Analysts, Inc. the global market for Testosterone Replacement Therapy (TRT) is projected to reach US $ 6.5 billion by 2020 (Global Industry Analysts, Inc., 2015). In this article, we aim to disentangle the possible reasons for such an apparently unjustifiable commercial success.

The promise of eternal youth and social accomplishment

During the twentieth century, life expectancy rose dramatically amongst the world's wealthiest populations. Moreover, continuous progress in the fields of medicine, nutrition, and public health have also allowed people to live the last part of life in good health. Such a feeling of well-being is the basis of many people's desire, despite their advanced age, to have a lifestyle comparable to that of much younger individuals. In this context, male rejuvenation, defined as a process in men to both limit the impact of ageing on body image and to experience greater virility, is growing among middle-aged and older men (Miner and Perelman, 2013). Simple and safe interventions such as weight reduction, smoking cessation, eating a balanced diet with five fruits and vegetables a day or a Mediterranean diet, and improving fitness, might help limit the effects of age (Khaw *et al*., 2008; Sofi *et al*., 2010).

However, clinical data suggest that men prefer the seemingly faster pharmaceutical approaches to 'rejuvenation' (Sigman, 2013). Since the production of many hormones decreases with age, it has been claimed that hormone replacement therapies might mitigate the effects of time (Morley, 2013). In this regard testosterone plays a key role. In fact, it is well known that

testosterone has androgenic effects, contributes to sex drive, and has anabolic effects, including the promotion of muscle mass, bone density, and maturation (Kloner *et al.*, 2016). Therefore, especially among western societies, there is a deep-rooted conviction that correcting a testosterone deficiency can restore all these conditions and reverse the effects of age. Thus, this hormone appears to be the much sought after hormonal fountain of youth, being evocative of virility, strength, and sexual vitality (Morley, 2013). Furthermore, thanks to its pivotal function in human interactions, testosterone is considered to be a 'social hormone' (Kirby, 2014). Accordingly, several authors argue that the role of testosterone might be best conceptualised as a motivator for elevated social status. Maintaining a high status position requires an increased sensitivity to aversive events and impending social threats, particularly those that challenge the high social status of an individual (Eisenegger *et al.*, 2011; Coates *et al.*, 2010; Kirby *et al.*, 2014). Testosterone appears to be able to influence such processes; in particular, it appears to confer high motivational drive, low fearfulness, and high stress resilience, either directly or via interactions with other hormones and neurotransmitter systems (Nyby, 2008; Kirby, 2014). In other words, testosterone is considered as responsible for success in contemporary societies that require individuals to be increasingly competitive in all areas of personal and working life often with their much younger counterparts. Its promised ability to delay or reverse ageing, and its social relevance, constitute the deepest reasons for testosterone success and constitute the psychological levers used to design successful marketing campaigns for 'Low-T drugs'.

The direct marketing campaign

Direct marketing campaigns play a key role in the success of testosterone products. Traditional drug promotion strategies are designed to influence physician prescription practices and include: the activities of pharmaceutical sales representatives, the donation of free drug samples and various gifts marked with the name of the drug itself, invitations to educational and promotional

meetings, and the distribution of promotional documents highlighting a drug's benefits in trials sponsored by the company (Kessel, 2014). However, the direct marketing strategy that is considered to be responsible for the success of 'Low-T drugs' is the so-called 'direct-to-consumer pharmaceutical advertising' (DTCPA). DTCPA can be defined as an effort by a pharmaceutical company to promote its prescription products directly to patients, and currently it is allowed only in the United States, New Zealand and partially in Canada (Abel *et al.*, 2006; Ventola *et al.*, 2011).

This strategy has grown rapidly over recent decades and it is now the most prominent type of health communication that the public encounters (Ventola *et al.*, 2011). The advertising of 'Low-T drugs' has a very wide target audience that includes men aged between 40 and 80 years who share one or more frequent symptoms: decrease in libido, lack of energy, sadness, grumpiness, tiredness after dinner, and the reduced ability to play sport (Singer, 2013). These adverts basically formulate a diagnosis. Indeed, they induce consumers to believe that they are affected by specific syndromes defined with catchy medicalised terms such as 'Low T' and 'andropause'. Consumers are persuaded by these sophisticated marketing techniques that their condition is due to testosterone deficiency, although it might be really caused by several non-hormonal factors or simply determined by the normal effects of advancing age (Braun, 2013; Singer, 2013; Perls and Handelsman, 2015). In other words, the ubiquitous 'Low-T drugs' DTCPA not only promote a drug but increasingly reframe and medicalise human traits to create a need for the drugs (Kessel, 2014). Proponents argue that DTCPA educates patients by making them aware of the existence and treatment of a condition and thus allowing them to take charge of their health (Connors 2009; Ventola 2011). However, the problem here is that consumers lack the technical expertise to critically evaluate the deceptively simplified medical science claims (Perls and Handelsman, 2015). As a consequence, 'Low-T drugs' DTCPA may set patients against their doctors, pressuring them for compliant prescribing on demand and distorting their clinical judgments (Perls and Handelsman, 2015).

The indirect marketing campaign

In parallel with direct marketing promotions, pharmaceutical companies sponsor their drugs through indirect marketing campaigns that are at least equally effective (Braun, 2013; Kessel, 2014). These methods of promotion are subtler as they convey messages with a more neutral tone, avoiding the explicit reference to a brand name (Braun, 2013). Their aim is to influence the opinion of physicians and of consumers about what conditions can be considered as diseases and when drugs are needed (Schwartz and Woloshin, 2013). In an interesting perspective on the argument, Braun, a medical writer, described his own experience of the process of the indirect promotion of testosterone replacement therapies (TRTs) for 'Low-T' (Braun, 2013).

The success of all indirect marketing campaigns for the promotion of 'Low-T drugs' is based on three strategies: lower the bar for diagnosis (turning ordinary life experiences into conditions that require medical diagnoses), raise the stakes so that people want to get tested, and spin the evidence about drug benefits and harms (Schwartz and Woloshin, 2013). Communication companies funded by pharmaceutical companies often coordinate these commercial initiatives. A widespread technique in this field is the practice of publishing articles in consumer magazines that are written by medical writers but signed by academic 'guest authors' who are asked to add their names without fulfilling the authorship criteria. In this case, 'guest authorship', is accompanied by 'ghost-writing', which occurs when a published article fails to acknowledge the original writer or the writers' contribution (Gøtzsche *et al*., 2009; Sismondo, 2009; Stern and Lemmens, 2011).

With regard to this practice, Braun reported his involvement in writing articles that adhered to the paradigm of 'Low-T' as a potentially serious condition for which new treatments were available (Braun, 2013). In trade magazines, the articles appeared under the by-line of a physician with no mention of the funder behind the overall marketing effort. This strategy considerably raised the value of the pieces because the reader perceived the information as objective and free of industry influence (Braun, 2013). The practice of ghost-writing within TRT seems to mirror the approach taken in the field of postmenopausal hormone therapy (HT) and, as a consequence, it is likely to produce the same results. Marketing messages in credible journals almost certainly

contributed to the widespread use of HT among millions of women who had no medical indication for the drug, acting in direct contradiction to the most important ethical rule of all physicians: 'first, do no harm' (Fugh-Berman, 2010).

Another common strategy of indirect marketing in the field of 'Low-T' is the pharmaceutical companies' sponsorship of educational materials for patients (Braun, 2013). Again, the goal here, is to raise awareness of a condition and the availability of a treatment, leaving the responsibility for the decision to the patient, who should ask his doctor if that specific product is the right remedy for him (Braun, 2013). Professional medical writers are also often asked to write consensus statements: conclusions that summarise meetings funded by pharmaceutical companies.

These recommendations are usually published as a guide to clinical practice. However, in this case, conflicts of interest can also influence the statement. In fact, the panel may not represent the true range of opinions that exist on the matter, either because the funders choose the panel members or because the organisers recruit panel members via the personal recommendations of key members (Braun, 2013). Accordingly, guidelines about 'Low-T' management, some of which are sponsored by manufacturers of testosterone products, have stretched the definition of hypogonadism to include functional disorders and unexplained low testosterone levels without any underlying well-defined pathology (Braun, 2013; Perls and Handelsman, 2015). Physicians also frequently use the monograph that results from the consensus conference when presenting continuing medical education lectures funded by pharmaceutical companies, inevitably influencing the audience prescribing behaviour (Braun, 2013).

Disease mongering

The criteria to diagnose LOH have been the focus of a heated debated for a long time. In fact, different symptoms appear at different testosterone threshold values. It is therefore very difficult to define a strict limit between normal and low testosterone (Huhtaniemi, 2014). The panel of experts

of the International Society for Sexual Medicine (ISSM) and a writing committee formed by the International Society for the Study of the Aging Male (ISSAM), the International Society of Andrology (ISA), the European Association of Urology (EAU), the European Academy of Andrology (EAA) and the American Society of Andrology (ASA) concluded that men with TT below 8 nmol/L are likely to have testosterone deficiency and, if their luteinizing hormone (LH) value resulted high, they recommend to initiate testosterone treatment. Moreover, in men with TT between 8 and 12 nmol/L and low T symptoms and/or a substantially elevated sex hormone binding globulin (SHBG) level, they suggest further evaluation and a trial of TRT once other causes of their symptoms have been excluded (Wang *et al.*, 2008; Dean *et al.*, 2015).

Testosterone cut-off levels suggested by the guidelines are in line with the results of European Male Ageing Study (EMAS). In this cross sectional study, Wu *et al.* used a reductive analytic approach to produce clinical and biochemical criteria for diagnosing LOH in order to prevent the excessive diagnosis of hypogonadism and the injudicious use of testosterone therapy in older men. They observed an increased number of sexual symptoms associated with a higher odds ratio for a decreased threshold value for total testosterone (8.0 to 11.0 nmol per liter). This association was further strengthened by the addition of free testosterone levels to the analysis. Authors concluded that LOH can be defined by the presence of three sexual symptoms (i.e. decreased frequency of morning erection, decreased frequency of sexual thoughts, erectile dysfunction) associated with a total testosterone level of less than 11 nmol per liter and a free testosterone level of less than 220 pmol per liter (Wu *et al.*, 2010). By applying these criteria, the overall prevalence of LOH in the EMAS study population would be 2.1%. The majority of these patients would benefit from weight-loss and lifestyle modification and only a small minority of them from testosterone treatment (Wu *et al.*, 2010).

Late onset-hypogonadism is thus a well defined condition, which appears to be mostly irreversible and able to determine a serious deterioration in health. Indeed, in a recent prospective observational cohort survey, Ahern *et al.* observed a return to normal testosterone values in only

4.3% of initially affected subjects per year of follow up. Moreover they reported a mortality rate in men with primary hypogonadism 2.5 fold higher than in the whole study population (Ahern *et al*., 2016). This is compatible with other previous findings which observed a substantially increased mortality among men affected by LOH (Araujo *et al*., 2011; Pye *et al*., 2014).

Despite the efforts to establish strict diagnostic criteria, LOH is constantly at risk of disease mongering, a phenomenon that widens the boundaries of treatable illness to expand markets for those who sell and deliver treatments (Moynihan *et al*., 2002). Both direct and indirect marketing campaigns fail to emphasize adequately the paramount importance of using the combination of biochemical measures and stringently defined, symptom-based criteria in order to diagnose LOH (Wu *et al*., 2010). Consequently, many patients who start testosterone replacement therapy don't really need it. This is not only inappropriate but also dangerous. In fact, each of the two criteria, when considered alone, doesn't have a pathological connotation. Symptoms may be simply the consequence of ageing and testosterone declines physiologically with increasing age at the rate of approximately 1% per year from the age of 30 (Wang *et al*., 2008; Perry *et al*., 2000; Morley, 2013). Noteworthy, in a study investigating the latter issue, Harman *et al*. observed that a substantial proportion of healthy men over 60 years of age have circulating testosterone concentrations in the range conventionally considered to be hypogonadal (Harman *et al*., 2001). Another problem that favours disease mongering is the poor adherence of physicians, especially in the US, to the clear guidelines of the treatment of male hypogonadism. As proof of this, the FDA found that testosterone level assessment prior to the initiation of treatment did not occur in 28% of men who received a new testosterone prescription (Nguyen *et al.*, 2015). These data suggest that only symptoms were extracted from the definition of LOH and that these symptoms are now used as unequivocal diagnostic elements in clinical practice.

Finally, the decline of testosterone concentration in the elderly population is often due to comorbidities such as obesity or chronic diseases. In this regard, the European Male Ageing Study (EMAS) reported that 75% of men with symptomatic hypogonadism were overweight or obese (Wu

et al., 2008; Wu *et al*., 2010; Pfaff and Joels, 2016). These people are often incorrectly considered as affected by primary LOH and are therefore treated with testosterone. Conversely, proper management should be aimed at addressing the underlying condition (Perls and Handelsman, 2015). In support of this, a longitudinal study showed that weight loss may be an effective means to normalize suppressed testosterone levels (Camacho *et al*., 2013).

Conclusions

Late onset hypogonadism is a rare but serious condition and affected men might respond favourably to testosterone treatment. However, the vast majority of men treated with testosterone replacement therapy don't need it. Reasons behind this extraordinary widening of indications for 'Low-T drugs' prescriptions are the testosterone properties evocative of eternal youth and social accomplishment, the direct and indirect marketing campaigns and the disease mongering of 'Low-T'. These mechanisms have managed to bypass the fundamental principles of evidence-based medicine. In fact, they have brought to success a product with an unknown risk-benefit ratio. The data on overuse are worrying: almost 95% of testosterone replacement therapy is prescribed in ways that are inconsistent with guideline recommendations (Jasuja *et al*., 2015; Morgan *et al*., 2016). This scenario inevitably produces a cascade of negative events. On the one hand, a lot of money is being wasted on unnecessary drugs and, on the other hand, other treatable diseases with similar symptoms are being ignored in favour of testosterone treatment (Kamerow, 2014). Even more alarming is that, according to rules currently in force, the 'Low-T drugs' campaign constitutes a successful promotion model that is applicable to any drug. Dangerously, our society constitutes a fertile ground for these commercial initiatives. In fact, we live in a sort of 'magic bullet' age, when people want a very simple solution to complex medical or ageing-related problems that does not involve them having to do any hard work, like modifying their lifestyle permanently.

Stricter regulations that control both direct and indirect marketing are probably necessary. However, more immediately, only the physicians' intellectual honesty can challenge this drift. In fact, prescription appropriateness is currently the simplest and most efficacious method to cause this diseased system to collapse.

Authors' roles

A.B. and P.V. conceived the study. A.B., E.S. and P.V. drafted the first version of the manuscript. E.S. actively revised the manuscript.

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