

1 **“FOREVER YOUNG” ***

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

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

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25 **Abstract**

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

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

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48 **Introduction**

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

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

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

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

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

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

98 be tested with adequately powered randomised controlled trials (Yeap *et al.*, 2014a; Yeap *et al.*,
99 2014b; Yeap *et al.*, 2016).

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

107 **The promise of eternal youth and social accomplishment**

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

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

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

141 **The direct marketing campaign**

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

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

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

170 **The indirect marketing campaign**

171 In parallel with direct marketing promotions, pharmaceutical companies sponsor their drugs
172 through indirect marketing campaigns that are at least equally effective (Braun, 2013; Kessel,
173 2014). These methods of promotion are subtler as they convey messages with a more neutral tone,
174 avoiding the explicit reference to a brand name (Braun, 2013). Their aim is to influence the opinion
175 of physicians and of consumers about what conditions can be considered as diseases and when
176 drugs are needed (Schwartz and Woloshin, 2013). In an interesting perspective on the argument,
177 Braun, a medical writer, described his own experience of the process of the indirect promotion of
178 testosterone replacement therapies (TRTs) for ‘Low-T’ (Braun, 2013).

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

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

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

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

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

217 **Disease mongering**

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

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

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

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

247 4.3% of initially affected subjects per year of follow up. Moreover they reported a mortality rate in
248 men with primary hypogonadism 2.5 fold higher than in the whole study population (Ahern *et al.*,
249 2016). This is compatible with other previous findings which observed a substantially increased
250 mortality among men affected by LOH (Araujo *et al.*, 2011; Pye *et al.*, 2014).

251 Despite the efforts to establish strict diagnostic criteria, LOH is constantly at risk of disease
252 mongering, a phenomenon that widens the boundaries of treatable illness to expand markets for
253 those who sell and deliver treatments (Moynihan *et al.*, 2002). Both direct and indirect marketing
254 campaigns fail to emphasize adequately the paramount importance of using the combination of
255 biochemical measures and stringently defined, symptom-based criteria in order to diagnose LOH
256 (Wu *et al.*, 2010). Consequently, many patients who start testosterone replacement therapy don't
257 really need it. This is not only inappropriate but also dangerous. In fact, each of the two criteria,
258 when considered alone, doesn't have a pathological connotation. Symptoms may be simply the
259 consequence of ageing and testosterone declines physiologically with increasing age at the rate of
260 approximately 1% per year from the age of 30 (Wang *et al.*, 2008; Perry *et al.*, 2000; Morley,
261 2013). Noteworthy, in a study investigating the latter issue, Harman *et al.* observed that a
262 substantial proportion of healthy men over 60 years of age have circulating testosterone
263 concentrations in the range conventionally considered to be hypogonadal (Harman *et al.*, 2001).
264 Another problem that favours disease mongering is the poor adherence of physicians, especially in
265 the US, to the clear guidelines of the treatment of male hypogonadism. As proof of this, the FDA
266 found that testosterone level assessment prior to the initiation of treatment did not occur in 28% of
267 men who received a new testosterone prescription (Nguyen *et al.*, 2015). These data suggest that
268 only symptoms were extracted from the definition of LOH and that these symptoms are now used as
269 unequivocal diagnostic elements in clinical practice.

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

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

278 **Conclusions**

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

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

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322 **Authors' roles**

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

324 E.S. actively revised the manuscript.

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331 **Conflict of interest**

332 None declared.

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