“Low T” (low testosterone level, aka hypogonadism) is high profile these days. Sales of testosterone replacement therapies (TRTs) for Low T have more than doubled since 2006 and are expected to triple to $5 billion by 2017, according to forecasts by Global Industry Analysts.1 Driving these sales is a sophisticated marketing effort to define low testosterone level as a disease for which the treatment is TRT. I know this because, as a professional medical writer, I have helped craft that message for transmission in a range of media to both physicians and consumers.

This is hardly the first time that an age-related condition has been spun into a disease state when a new product has been developed that is believed to alleviate or attenuate the condition. In fact, the current situation with TRT eerily echoes the way that hormone therapy was, for years, touted as a safe treatment for menopause-related symptoms and the prevention of cardiovascular disease in women.2 Only after the Women’s Health Initiative study found that older women using hormone therapy had small excesses in the incidence of breast cancer, myocardial infarction, cerebrovascular accident, and venous thrombosis did physicians become more cautious about prescribing it and limit its use to appropriate female patients.3

An examination of the current ways that industry is reshaping the paradigm of Low T is warranted now not simply because of the potential public health risks associated with widespread use of TRT in the absence of a Women’s Health Initiative–scale study. Efforts have been made in recent years to curtail the abuses of pharmaceutical influence4 and encourage greater transparency in medical communications.5 As this article demonstrates, these efforts, although salutary, do not fundamentally alter the influences of drug company funding on the content and tone of messages directed at physicians and consumers.

Ghostwritten Articles for Consumer Magazines

In 2009, a well-known endocrinologist was contacted by the public relations firm HealthSTAR Communications. The firm had been hired by a pharmaceutical company to place articles in popular magazines that would appear under the byline of physicians who could talk about the “hazards” of low testosterone levels and the availability of new forms of TRT. The endocrinologist forwarded me the e-mail from the public relations firm requesting that he write a short article for Life After 50 magazine. The e-mail included a “Facts for Women” sheet that encouraged women to “diagnose” their male partners and urge them to seek medical attention (because men, demonstrably, do not seek such attention as much as they should). The fact sheet included the URL for a consumer-oriented website created by Abbott Laboratories.6

I wrote a brief, neutral-sounding article, put the physician’s name on it, and sent it off. In the following months, the physician was contacted by HealthSTAR Communications for more articles, or just quotes that could be passed on to a magazine writer. I generated versions of the original article, also to appear under the physician’s byline, for Woman’s Day, Business Week, Positive Change, and Health View. (I was paid for all of these articles by the physician himself—I do not know whether he was being paid by either the public relations firm or a drug company.) Although these articles were relatively neutral in tone and did not mention specific products, none were skeptical, none questioned the reliability of the data on which claims were being made, and none included the views of clinicians who dissented from the emerging paradigm about Low T. In part, that was because I was just learning about the issue myself and had not dug deeply into the literature. But I also knew what I was getting paid to do: trumpet the party line. As a result, the articles adhered nicely to the new paradigm of Low T as a potentially serious condition for which new treatments were available. The fact that the articles appeared under the byline of a physician and appeared in trade magazines with no mention of the funder behind the overall effort raised the marketing value of the pieces considerably because it is likely that readers trust information that appears to be objective and free of industry influence.

Patient Education Materials

In 2010, I was hired by a medical communications company to write a consumer-level booklet about low testosterone levels and TRT. The
project was funded by Solvay, original maker of AndroGel testosterone gel, 1.62% (later purchased by Abbott Laboratories). To my surprise, Solvay did not try to blatantly spin the copy to favor Androgel. Quite the opposite. The Solvay team reviewing the first draft often made changes that made the booklet more neutral.

For example, I had initially written the following sentence in an early draft: “You can increase the positive effects of TRT on your overall health by taking a few basic steps.” The reference to TRT was removed by the Solvay medical-legal reviewing team, and the sentence was changed to “You can improve your overall health by taking a few basic steps.”

This was not altruism, however. It was astute legal caution. Pharmaceutical companies face a real threat of litigation arising from unsubstantiated marketing claims, as well as regulatory discipline from the US Food and Drug Administration. It is in their interest, therefore, to play it safe with all claims and to avoid the overt peddling of a brand or product. Instead, the goal is to raise awareness of a condition and the availability of a treatment, leaving the responsibility for a decision to the patient, who should “talk to your doctor to see if X might be right for you.”

In the end, the patient education booklet was both blandly accurate and effective in transmitting the company’s core messages to tens of thousands of patients. Here, for example, is part of the booklet’s conclusion:

You’ve seen that the hormone testosterone is important throughout life. A simple blood test can show if you have low testosterone, and a visit with your doctor can confirm whether or not you have hypogonadism. If so, you can choose from several options to deliver testosterone to your blood. Doing so may relieve your bothersome symptoms and may help restore your energy, positive mood and sexuality.

The passage is true, primarily thanks to the liberal use of the words “can” and “may,” which are often suggested by legal review teams because they allow the wiggle room required in legal defenses. And yet the passage is also far from the whole truth. Despite my own best intentions (and training as a journalist), it is a shill for the sponsor—an unneutral, unbalanced presentation of “facts” that serves primarily to drive people to their physicians seeking the holy grail of “energy, positive mood, and sexuality” in the form of testosterone.

“Consensus” Panel Statements

In 2012, I was hired by a professional physicians’ organization to attend a meeting of experts in the field of hypogonadism and to write a summary of the meeting’s conclusions—a “consensus statement”—to be published as a guide to clinical practice. In this case, consensus was not difficult to achieve because the panel members shared a basic perspective on the value of TRT (although some differences of opinion on technical matters existed).

The meeting was funded by Abbott, and every panel member had served as either a consultant or researcher for Abbott or other companies with TRT products on the market or in the pipeline (ie, Auxilium, Endo Pharmaceuticals, and Lilly). Abbott’s role as sponsor and the potential conflicts of interest of all panel members were acknowledged in the final printed monograph, as was my involvement as writer.

In writing the monograph, I included as much cautionary or qualifying language as I could, based on my own much deeper knowledge about this subject. Some of this language survived the rounds of review and editing that followed. For example, to balance the claim that low testosterone levels are associated with higher mortality (an association that has appeared more than once in the literature), I noted that a recent systematic review and meta-analysis had found large between-study differences in results and methodological problems that cast doubt on the claimed association.

But other sections or sentences of a cautionary nature were deleted by panel members during the review process. Here are 2 that were cut:

It is worth noting that the quality of the evidence on which current clinical guidelines for TRT are based is low or very low, and that similar guidelines about the alleged benefits of hormone therapy for post-menopausal women have been questioned after high-quality studies of sufficient size and duration were carried out.

Composite measures of T levels and the symptoms related to low circulating androgens are likely to be fluid and lack stability over long periods of time. This suggests that Symptomatic Androgen Deficiency (SAD) represents a transient, rather than a permanent, state for the majority of the general male population and may cost doubt on the use of SAD or similar constructs as proxies for true age-related hypogonadism.

If those paragraphs had remained, they would have helped balance the tone of the resulting monograph. That does not mean that the monograph is hopelessly biased. In fact, I believe that it is more cautionary than some guidelines I have read and that it contains an up-to-date summary of treatment options that nonspecialists might find useful. At the same time, I believe that the overall perspective of the piece is, at best, neutral on the potential clinical utility of TRT and on the larger potential risks posed by widespread use of TRT by eugonadal men. I believe that a more sharply skeptical tone is warranted by the existing data—or lack thereof.

A potential weakness of the consensus panel model for generating clinical practice recommendations is that some panelists work harder than others. Some attendees of the hypogonadism meeting, for example, were careful, responsible, and fair minded, both during the meeting and in the reviewing of monograph drafts. Others did a far more cursory job, and 1 member did not participate in the review process at all. Such variability in effort may be inevitable, but it can result in so-called consensus statements that actually reflect only the strongly held views of a minority of the panel. In addition, of course, a panel as a whole may not represent the true range of opinions that exist on a matter of interest, either because the members are suggested by the funder or because the organizers recruit panel members via the personal recommendations of key members. (Some companies that organize consensus panels are attempting to improve transparency. One of my clients, New England Research Institutes, actively seeks a diversity of opinion among panel members and requires the participation of an independent panelist whose role is to flag imbalance or favoritism appearing in the conference itself or whatever papers or materials arise from it.)

A final point: the monograph resulting from the hypogonadism “consensus conference” was published in 2012 and given continuing medical education credit. I created a PowerPoint slide show based on the monograph that was used by physicians who presented Abbott-
Mr Ferguson, a healthy 55-year-old man without active problems, is in your office for his annual checkup. He tells you that he has no problems and feels fine.

“Well,” his wife chimes in, “he has been a little grumpy. Especially since Sammy—our son—starting beating Shaun here in their one-on-one basketball games.”

“Of course, I’m grumpy. We bet on a game and now I have to do the lawn,” Shaun says, shaking his head. “Takes forever, and it’s exhausting.”

“I understand,” you reply, laughing. “So, are you still off cigarettes?”

“Wait,” his wife blurts out before Shaun answers. She stares. “Don’t you think he needs a blood test? Could this...
be...Low T?” She hands you a paper—Shaun has completed the Low T question quiz from the Is It [Low T?] website.2

Testosterone usually brings sex to mind. Curiously, only 2 of 10 quiz questions are about sex: Decreased libido? Erections less strong? Your patient did not check either. But he checked 3 about energy, mood, and sports performance, enough for the quiz to suggest asking his doctor about “Low T” (low testosterone level, aka hypogonadism).

The site also offers strategies for spouses to “motivate the men in their lives to talk to their doctors.” For example, if the man says “I don’t have much energy anymore,” “[his spouse might think] he’s just making excuses.” But the site tells her that Low T may be the real issue because it can affect energy levels—never suggesting other explanations such as stress, depression, or other medical problems.

The Low T website is part of a broader disease awareness campaign run by Abbott Laboratories, maker of Androgel, the leading testosterone replacement product (>3 million prescriptions and >$1 billion in sales in the United States in 2012).2

Whereas traditional drug promotion such as direct-to-consumer ads, physician samples, gifts, and detailing has received much attention, far less is known about disease awareness campaigns—much broader efforts to influence how physicians and the public think about what constitutes disease and when drugs are needed. These well-coordinated campaigns are more subtle than drug-specific campaigns, and they blur the line between public health or professional education and marketing.

The article by Braun6 on the promotion of Low T is a fascinating and troubling first-hand look inside the kitchen of industry disease awareness campaigns. Braun exposes how industry used ghost-written magazine articles under a celebrity physician’s byline. This is on top of educational campaigns, television and magazine ads, and mobilizing industry-funded advocacy groups. The campaigns also target physicians through special journal supplements, consensus statements, and continuing medical education, as Braun also highlights.

The Low T campaign provides a template for understanding how disease awareness campaigns work. Like other campaigns (eg, Bipolar Disorder and Restless Legs Syndrome), the Low T campaign uses 3 basic strategies: lower the bar for diagnosis (turning ordinary life experiences into conditions that require medical diagnosis), the Low T campaign run by Abbott Laboratories, maker of Androgel, the leading testosterone replacement product (>3 million prescriptions and >$1 billion in sales in the United States in 2012).

Whereas traditional drug promotion such as direct-to-consumer ads, physician samples, gifts, and detailing has received much attention, far less is known about disease awareness campaigns—much broader efforts to influence how physicians and the public think about what constitutes disease and when drugs are needed. These well-coordinated campaigns are more subtle than drug-specific campaigns, and they blur the line between public health or professional education and marketing.

The article by Braun6 on the promotion of Low T is a fascinating and troubling first-hand look inside the kitchen of industry disease awareness campaigns. Braun exposes how industry used ghost-written magazine articles under a celebrity physician’s byline. This is on top of educational campaigns, television and magazine ads, and mobilizing industry-funded advocacy groups. The campaigns also target physicians through special journal supplements, consensus statements, and continuing medical education, as Braun also highlights.

Lower the Bar
Health exists along a spectrum. At one end, people are clearly well; at the other, clearly sick. What about the big gray zone in between? When do bothersome experiences become symptoms? Where do you draw the line? For Low T, the location of the line is implausible. Everyone feels a little tired—or sad or grumpy—sometimes. And everyone slows down a bit over time (it is called aging). Recent US endocrinology8 and European urology8 guidelines actually recommend against using such Low T-type quizzes because they are unreliable and unvalidated. The Endocrine Society guideline goes even further, recommending against general population screening for Low T “because of the lack of consensus on a case definition and the extent to which androgen deficiency is an important health problem.”9(p2543)

Interpreting laboratory values is all about lines—often determined statistically: lines are typically drawn, for example, 2 standard deviations beyond the mean, defining 5% of the population as abnormal. If the lines are drawn closer to the mean of normally distributed values, the proportion defined as abnormal expands rapidly. For testosterone, a serum level of 230 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) defines 7% of men 50 years and older as abnormal; moving the line to 350 ng/dL (the cutoff for “normal” used in the consensus recommendation coauthored by Braun6) increases the abnormal proportion to 26%.

Ideally, the line would be drawn to maximize benefit and minimize harm. Unfortunately, lines are often drawn not because of evidence but to expand the market. Whether or not broad disease definitions are in the public’s interest, they do serve the financial and professional interests of industry, specialists, and advocacy groups.

Raise the Stakes
It is one thing to tell men that Low T can make them grumpy; it is another to say that it can kill them. Messages raising the stakes about Low T have Low T, ED can sometimes have Low T. Although the majority of men with ED do not have Low T, ED can sometimes be due to low testosterone.”

Table. Claims From isitlowt.com9

<table>
<thead>
<tr>
<th>Claims From isitlowt.com9</th>
<th>Randomized Trial Evidence of TTa</th>
<th>Unknown Effectb</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Unwanted Body Changes:</em></td>
<td>Increased lean body mass (2.7 kg), decreased fat mass (~2.0 kg), and no change in body weight vs placebo; Increased bone density in lumbar spine ~2%, No change in femoral neck; Increased grip strength (3.3 kg) and inconsistent effect on lower extremity strength or physical function</td>
<td>Effect on fractures or falls</td>
</tr>
<tr>
<td><em>Decreased Energy:</em></td>
<td>No trials identified specifically assessed energy or fatigue</td>
<td>Meaningful improvement in energy level or ability to do routine tasks</td>
</tr>
<tr>
<td><em>Mood Changes:</em></td>
<td>Inconsistent effect on depressive symptoms</td>
<td>Meaningful improvement in depressive symptoms</td>
</tr>
<tr>
<td><em>Reduced Sex Drive:</em></td>
<td>Moderate increase in libido; Possible small increase in overall sexual satisfaction</td>
<td>Meaningful improvement in overall sexual satisfaction</td>
</tr>
<tr>
<td><em>Sexual Dysfunction:</em></td>
<td>Small increase in satisfaction with erectile function</td>
<td>Meaningful change in erectile dysfunction</td>
</tr>
</tbody>
</table>

Abbreviations: Low T, low testosterone level; TT, testosterone therapy.
T have appeared regularly in scientific meeting reports and journal articles and often make their way into the news ("Low testosterone could kill you," according to ABC News).

Because Low T becomes more common with aging, associations with death are inevitable. But these associations come from inherently weak observational studies that cannot exclude residual confounding or establish causality. To his credit, Braun was able to highlight these fundamental limitations in the consensus recommendations that he coauthored. Ironically, the same report asserts that Low T increases the risk of heart disease even though this finding is based on similarly limited research (in fact, a randomized trial of testosterone therapy in elderly men was stopped early because it increased the risk of cardiovascular disease).

Spin the Evidence

The implicit message of the Low T awareness campaign is that testosterone therapy will improve men’s energy, mood, and sex life. Neither the Low T website, nor the consensus recommendation, nor the magazine articles published using unnamed ghostwriters tell readers which outcomes are likely to improve with testosterone therapy—let alone the magnitude of the changes. The focus is on getting a diagnosis and on which form of treatment to take.

Physicians and patients who assume that treatment has an important effect on all or most symptoms may be surprised by the evidence from randomized trials (Table: Testosterone therapy results in only small improvements in lean body mass and body fat, libido, and sexual satisfaction, and has inconsistent (or no) effect on weight, depression, and lower extremity strength. Whether these effects are big enough to matter to patients is unknown. Nor is it known whether they are big enough to outweigh the harms of testosterone therapy, ie, polycythemia that may increase thromboembolic events, edema, serious hepatotoxic effects, gynecomastia, worsening of sleep apnea, prostate enlargement, and rise in prostate-specific antigen level (and potential increased risk of prostate cancer).10

We agree with Braun that there is a strong analogy between the marketing of testosterone therapy for men and estrogen therapy for menopausal women. Ignoring the lessons of estrogen therapy is scandalous. Before anyone makes millions of men aware of Low T, they should be required to do a large-scale randomized trial to demonstrate that testosterone therapy for healthy aging men does more good than harm.

ARTICLE INFORMATION

Author Affiliations: VA Outcomes Group, Department of Veterans Affairs Medical Center, White River Junction, Vermont (Schwartz, Woloshin); Center for Medicine and the Media, Dartmouth Institute for Health Policy and Clinical Practice (Schwartz, Woloshin); Norris Cotton Cancer Center, Lebanon, New Hampshire (Schwartz, Woloshin).

Corresponding Author: Dr Woloshin, Department of Veterans Affairs Medical Center, White River Junction, VT 05009 (steven.woloshin@dartmouth.edu).


Conflict of Interest Disclosures: None reported.

Disclaimer: The opinions expressed by the authors of this Invited Commentary are their own, and they should not be interpreted as official positions of the Department of Veterans Affairs.

Additional Information: Drs Schwartz and Woloshin are members of the Steering Committee for the Preventing Overdiagnosis conference cosponsored by the Geisel School of Medicine at Dartmouth in September 2013.

Additional Contributions: We thank Stephen Colbert for bringing needed attention to the selling of Low T and Victor Montori, MD, for reviewing the Table.

REFERENCES