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TESTOSTERONE THERAPY

LABELING

Studies linking testosterone therapy and cardiac events have generated a number of suits, and this figure is likely to grow, attorney Brett A. Emison says in this BNA Insight. The author discusses the science behind the claims, which allege men are pressured into unnecessary testosterone therapies due to the industry's aggressive marketing and use of off-label prescriptions. He also offers comparisons to the hormone replacement therapy litigation that preceded it.

Testosterone Therapy: Litigation Commences After Studies Link Hormone to Heart Attack, Stroke

BY BRETT A. EMISON

Testosterone replacement therapy (TT) has seen remarkable growth in recent years following aggressive marketing promising to help aging men improve their energy levels and low sex drive. Abbott, for instance, with category-leading AndroGel, has had annual sales of $600 million of its therapy gel.[1] Industry-wide, annual prescriptions for testosterone increased five fold from 2000 to 2011. Sales of testosterone replacement therapies are expected to reach $5 billion within the next three years.[2]

Reports, however, suggest that many men may have needlessly received testosterone therapies due to the industry's aggressive marketing and use of off-label prescriptions. Even worse, studies published in 2013 and 2014 suggest that testosterone gels might double—or even triple—the risk of heart attack for some men. In turn, the U.S. Food and Drug Administration announced Jan. 31 that it will review the therapies' safety.

To date, there have been only a handful of cases filed. Anyone in the media or other channels hazarding a guess as to how many potential lawsuits will be filed, are doing just that—guessing. But with more than 5 mil-

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[1] "Off-label marketing: How testosterone replacement got big," Chris Adams, McClatchy Newspapers. June 13, 2011. http://www.mcclatchydc.com/2011/06/13/115719/off-label-marketing-how-testosterone.html. Abbott recently spun off its AndroGel division (and other areas) into a new company, AbbVie.

[2] Are Testosterone Drugs the Next Viagra?, Shannon Pettypiece, Bloomberg Business Week, May 10, 2012. http://www.businessweek.com/articles/2012-05-10/are-testosterone-drugs-the-next-viagra.

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lion men across the country having received various forms of testosterone therapy (TT), the potential for mass torts litigation is substantial. The types of claims filed will likely focus on two primary allegations: (1) manufacturers' off-label marketing and promotion of the hormone drugs to men who are not actually candidates for the treatment; and (2) dangerous side effects of the hormone therapy that include cardiac event(s) such as heart attack and stroke and the failure of manufacturers to warn of these complications.

Off-Label Marketing of Testosterone

Testosterone supplements have been approved by the FDA for limited specific conditions caused by documented low testosterone levels or ''Low T.'' Despite the limitation, testosterone prescriptions doubled in just four years between 2008 and 2012 due largely to aggressive advertisements from testosterone makers directly targeting men.[3] But with off-label marketing, many men have received testosterone replacement therapy without Low T levels and for unapproved uses. In recent years such off-label use has included fatigue and diminished libido. CBS News reported that nearly 43 percent of men who have received testosterone therapy actually had a normal hormone level.

Making matters worse, once testosterone therapy starts, patients may not be able to stop. ''Once you start, your body begins shutting down natural production of the hormone, thinking it's no longer needed,'' said Dr. Gregory Broderick.[4] A 2011 report in the magazine Men's Journal reached the same conclusion.[5]

A McClatchy News report suggested that AndroGel's marketing was positioned to make the treatment ''ride (the) coat tails of Viagra.''[6] But unlike Viagra, AndroGel was never approved by the Food and Drug Administration to treat erectile dysfunction. Instead, AndroGel, like other testosterone therapies, was approved to treat a relatively specific condition of the sex glands called hypogonadism. According to a significant whistleblower lawsuit, AndroGel's manufacturer[7] wanted to boost its sales with an aggressive strategy to push ''off-label''—or unapproved—uses of the drug. Indeed, AndroGel has gained about 50 percent market share.

Researchers have expressed concern over the off-label prescription of testosterone therapy, noting that a ''fall in hormone levels in both men and women is a normal part of aging; it is not necessarily a disease. Making it into a disease may end up causing more harm than good.''[8]

A pair of articles in *JAMA Internal Medicine* last August drew attention to the marketing efforts of testosterone therapy, where the strategy of ''creating a crisis'' was discussed. In summary, the articles suggested that promotional campaigns for testosterone therapy were disguised as what appeared to be objective physician papers but were actually paid for by drug companies, and then edited or even distorted to fit the company's agenda, and, worse, that the ''disease'' of Low T was created solely as a marketing ploy.

''There are a lot of American men. Some are grumpy. Some are tired. Some may not even be interested in sex at the moment. And all of them are aging. This is the intended audience for the Low T campaign. Whether the campaign is motivated by a sincere desire to help men or simply by greed, we should recognize it for what it is: a mass, uncontrolled experiment that invites men to expose themselves to the harms of a treatment unlikely to fix problems that may be wholly unrelated to testosterone levels.''[9]

According to one doctor, the Low T marketing campaign has been simple and uses three basic 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.''[10]

And how did the drug makers do this? One tactic was to solicit favorable articles and columns recommending the treatment that would appear to be objective, scientific articles but were, in fact, ''an uncritical, unbalanced presentation of 'facts' that serve[d] primarily to drive people to their physicians seeking the holy grail of 'energy, positive mood, and sexuality' in the form of testosterone.''[11] Said one medical author:

> I. . . knew what I was getting paid to do: trumpet the party line. . . . 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.[12]

''I can't underscore enough how important off-label sales were,'' said John King, a former sales manager. ''You can do the math: If we had truly stuck to the FDA approved indication, AndroGel would never have had anywhere near the sales it had.''[13]

Increased Risk of Heart Attack

Following the aggressive, off-label marketing of testosterone, and recent studies linking testosterone

[3] ''Testosterone supplements linked to heart attacks in new study,'' Jonathan Lapook, CBS News, January 29, 2014. http://www.cbsnews.com/news/testosterone-supplements-linked-to-heart-attacks-in-new-study/.

[4] ''Baby Boomers Find Youth in Testosterone,'' Jacque Wilson, CNN, November 17, 2012. http://www.cnn.com/2012/11/16/health/baby-boomers-testosterone/.

[5] ''The Testosterone Dilemma,'' Daniel Duane, Men's Journal, November 2011. http://www.mensjournal.com/magazine/the-testosterone-dilemma-20121122.

[6] ''Off-label marketing: How testosterone replacement got big,'' Chris Adams, McClatchy Newspapers, June 13, 2011. http://www.mcclatchydc.com/2011/06/13/115719/off-label-marketing-how-testosterone.html.

[7] AndroGel has been through a number of corporate owners in the last decade. United Pharmaceuticals was bought by Solvay Pharmaceuticals (which was then bought by Abbott Laboratories). Abbott spun off the division housing AndroGel into AbbVie, a new biopharmaceutical company composed of Abbott's former proprietary pharmaceutical business.

[8] Testosterone Tx Tied to Worse Cardiac Outcomes,'' Elizabeth DeVita Raeburn, MedPage Today, November 6, 2013. http://www.medpagetoday.com/Cardiology/PCI/42747

[9] Schwartz, Lisa MD and Woloshin, Steven MD, ''Low 'T' as in 'Template'; How to Sell Disease.'' JAMA Internal Medicine, 2013; 173(15):1460-2.

[10] *Ibid.*

[11] Braun, Stephen R., Promoting ''Low T'': A Medical Writer's Perspective, JAMA Internal Medicine, 2013; 173(15):1458-60

[12] *Ibid.*

[13] *Ibid.*

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supplements to heart attack, stroke, and other cardiac events, the FDA will reassess the risks of this treatment. ''We have been monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy,'' the FDA said in its statement.

The most recent study, published Jan. 29, 2014, by PLoS One,[14] and led by William D. Finkle, found that men aged 65 and older had double the risk of heart attack within 90 days of taking a testosterone gel when compared with non-testosterone users. For younger men (under 65) with a previous heart attack, testosterone gels increased the risk of a subsequent heart almost tripled within 90 days of starting testosterone gel. Dr. Finkle said his study was prompted by a 2010 report in the *New England Journal of Medicine*. The 2010 study involved a clinical trial of testosterone gel in men over 65 years old, and was halted after discovery of an increase in heart attacks and other heart issues in the group of participants using the testosterone replacement gel.

Dr. Finkle's group in their PLoS One study briefly addressed some research that preceded their own on the topic:

> More relevant perhaps is the rapid increase with age in the prevalence of diagnosed and undiagnosed coronary artery disease reported from autopsy studies, both overall and among accident victims, so that advanced age may be a more sensitive indicator of coronary disease prevalence than prior diagnoses. The recent study of TT within the VA healthcare system detected no change in the rate ratio for TT and coronary disease in the presence of existing coronary disease. However, since that study had less than 200 men with normal coronary arteries, they likely had insufficient statistical precision to address this question. Overall, our own findings appear consistent with a higher frequency of thrombotic events following TT prescription among men with more extensive coronary vascular disease. . . . Taken together, the evidence supports an association between testosterone therapy and risk of serious, adverse cardiovascular-related events—including non-fatal myocardial infarction—in men. [15]

A 2013 study published in the Journal of the American Medical Association (JAMA), also found that testosterone therapy resulted in a substantially increased risk for heart attack and stroke in men over 65. This JAMA study involved more than 8,700 men treated through Department of Veterans Affairs health care with a total testosterone level less than 300 ng/dL.[16]

More than 1,200 patients in the JAMA study examined had been given testosterone therapy. Among the men studied, 19.9 percent of those without testosterone therapy suffered death, heart attack or stroke. However, 25.7 percent of those taking testosterone supplements suffered death, heart attack, or stroke, representing a nearly 30 percent increase in risk-factor.[17]

What Labels Are Affected

Though AndroGel is clearly the industry leader in terms of annual sales, testosterone therapy is marketed under a number of brand names. Some testosterone treatments include:

- AndroGel
- Androderm
- Axirom
- Bio-T-Gel
- Delatestryl
- Depo-Testosterone
- Fortesta
- Striant
- Testim
- Testopel

Similarities to 'Hormone Replacement for Men'

The testosterone therapy litigation in its early stages has many similarities to the ''hormone replacement therapy'' (HRT) litigation that preceded it. After all, testosterone therapy is just hormone replacement for men. In both cases (as well as in other mass tort predecessors) we have a drug/therapy/treatment that becomes popular in the general public. Once a substantial number of patients begin using the treatment, research studies are conducted to test the treatment's safety and efficacy. When studies show a risk of harm, other studies follow. Some are commissioned by the drug manufacturers and others are published by third parties.

The number of lawsuits in the HRT litigation was substantial. Pfizer alone was named in over 10,000 suits over its HRT drugs including Prempro. This led to nearly $896 million in payments to settle 60 percent of its cases from women alleging their cancer was caused by the HRT.[18] The HRT litigation was based, in part, on an in-depth study published in the Journal of the American Medical Association in 2010 which showed that women who underwent hormone replacement therapy were at an increased risk of breast cancer. This study involved 12,000 women over a course of 11 years.[19]

And, again drawing similarities to testosterone therapy, the HRT litigation focused, in large part, on aggressive marketing to women, who naturally have biological processes that are ''supposed'' to occur. With the onset of puberty, a woman's ovaries produce natural hormones estrogen and progesterone. The hypothala-

[14] Finkle W.D., Greenland S., Ridgeway G.K., Adams J.L., Frasco M.A., et al. (2014) Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men. PLoS ONE 9(1): e85805. doi:10.1371/journal.pone.0085805.

[15] Finkle, et al. at 4-5.

[16] Vigen R, O'Donnell CI, Barón AE, et al. Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels. JAMA, 2013; 310(17):1829-1836. doi:10.1001/jama.2013.280386.

[17] *Ibid.*

[18] Feeley, Jef, ''Pfizer Paid $896 Million in Prempro Settlements,'' Bloomberg News, June 19, 2012.

[19] Chlebowski R.T., Anderson G.L., Gass M., et al. Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women. JAMA. 2010; 304(15):1684-1692. doi:10.1001/jama.2010.1500.

mus and pituitary glands send messages to the follicle (eggs encased in their sacs) to produce hormones.

In women as in men, the production of hormones slows over time. Around age 35 or earlier, a woman's hormone production has dropped considerably. Progesterone is the first hormone to decline and drops 120 times more rapidly than estrogen.

Menopause is the body's process of phasing out the reproductive cycle by reducing natural estrogen. In the average woman's reproductive life, menopause occurs when she is relatively young, usually between 46 and 62. During menopause, a woman's estrogen level drops sharply.

HRT refers to either the use of the combination of conjugated estrogens (estrogen) and progesterone (progestin), or the use of estrogen by itself. A focus of HRT litigation has been the combination use of estrogen and progestin.

Wyeth's ''cure'' for menopause symptoms was extolled by Dr. Robert Wilson, a New York gynecologist who wrote an article published in the Journal of the American Medical Association (JAMA). This article claimed that taking estrogen during menopause reduces breast and genital cancers, but then Wilson, through his popular book, *Feminine Forever*, claimed that menopause did not need to be a natural stage of life. What his book did not divulge was that its research and writing was bankrolled by Wyeth.[20]

Wyeth created a demand for Premarin (and later Prempro) by overpromotion and aggressive marketing, particularly for off-label uses. Wilson denied that menopause is a phase of life. Instead, he characterized it as a disease. Wilson claimed that estrogen was the cure for ''the tragedy of women.'' Menopause, he declared in the book, caused women to lose their youthful appearance and lose their sexuality.[21]

Much of the HRT marketing strategy is similar to how Abbott and others organized a campaign to convince men that their symptoms were not ordinary symptoms of aging, but a new ''disease.''

Like some testosterone manufacturers, Wyeth in its HRT campaign engaged a ghost-writer to promote hormone replacement therapy for women via medical journals. For both HRT and testosterone marketing, the goal was to publish widely with the appearance of objectivity and independence, and to allay patient fears. In fact, HRT marketing led to

> over 50 peer-reviewed publications, more than 50 scientific abstracts and posters, journal supplements, internal white papers, slide kits, and symposia. . . . [22]
>
> Between 1997 and 2003, DesignWrite's output for Wyeth on the Premarin family of products included . . . publications, . . . abstracts and posters, journal supplements, internal white papers, slide kits, and symposia. . . . Primary publications (articles that report clinical trials) ghostwritten by DesignWrite included four manuscripts on the HOPE trials of low-dose Prempro, for which DesignWrite was paid US$25,000 each. Secondary publications (articles that follow clinical trial reports and contain 'subsequent analyses, and reviews of the drug and its field of use') included 20 review articles that DesignWrite was assigned to write in 1997 for $20,000 each, a price that later rose to $25,000. Abstract production cost $4,000. DesignWrite charged $10,000 for editing manuscripts and $2,000 for editing abstracts 'written by author or other agency.' [23]

As part of its publication planning, Wyeth's Marketing Department convened monthly meetings to discuss publication strategies, draft outlines, and sometimes adjust the overall publication plan. In 2002, for example, Wyeth management ''charged the Publication Committee with increasing the number of positive HRT/Premarin-related publications. They have asked us to publish at least 1 study per month.''

Conclusion

The recent studies published by the Journal of the American Medical Association and the Public Library of Science (PLOS) have identified a serious scientific link between testosterone therapy and cardiac events including heart attack and stroke. A number of lawsuits have already been filed, though this is likely just the beginning.

Like the earlier HRT litigation, the testosterone litigation has focused on the manufacturer's aggressive, off-label marketing and undisclosed side effects. The early testosterone suits have asserted that Abbott and AbbVie ''deceived potential AndroGel users by relaying positive information through the press, including testimonials from retired professional athletes,'' and statistics suggesting a widespread need for the drugs, ''while downplaying known adverse and serious health risks,'' according to the complaints filed in February 2014.[24] As the market for these products continues to grow, there will likely be a number of complaints filed alleging cardiac injuries following testosterone therapy.

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[20] JNCI J Natl Cancer Inst (2002) 94(15): 1117.doi: 10.1093/jnci/94.15.1117.

[21] *Ibid.*

[22] Fugh-Berman A.J. (2010), The Haunting of Medical Journals: How Ghostwriting Sold ''HRT,'' PLoS Med 7(9): e1000335. doi:10.1371/journal.pmed.1000335.

[23] *Ibid.*

[24] ''Abbott Labs Sued by Five Men Claiming Androgel Injuries,'' Andrew Harris, Bloomberg News, February 5, 2014. http://www.bloomberg.com/news/2014-02-05/abbott-labs-sued-by-five-men-claiming-androgel-injuries.html

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