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EXPERT ANALYSIS

Testosterone Therapy: Litigation Begins After Studies Link Hormone to Heart Attack And Stroke

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Testosterone-replacement gels have seen remarkable growth in recent years as the result of aggressive marketing promising to help aging men improve their energy levels and low sex drive. For instance, Abbott Laboratories has had $600 million in annual sales of AndroGel, its category-leading therapy gel.[1]

From 2000 to 2011, industry-wide annual prescriptions for testosterone in the United States increased by a factor of five, to 5.3 million. Sales of testosterone-replacement therapies are expected to reach $5 billion by 2017.

However, reports suggest that many men may have needlessly received testosterone therapy, or TT, because of the industry's aggressive marketing and for prescriptions for "off-label" uses not approved by the U.S. Food and Drug Administration. In 2012, U.S. drug companies spent more than $3.4 billion to advertise testosterone gels directly to consumers.[2]

Studies published in 2013 and 2014 suggested that testosterone gels might double — or even triple — the risk of heart attack among some men. In turn, on Jan. 31, 2014, the FDA announced that it would review the safety of these agents.

As of this writing, only a handful of cases have been filed. Anyone in the media or other channels who estimates how many potential lawsuits will be filed is just guessing. Since more than 5 million men across the country have received various forms of testosterone therapy (the most common of which is testosterone gel), the potential for mass tort litigation is substantial.

The types of claims filed will probably focus on two primary allegations:

- Manufacturers' off-label marketing and promotion of the hormone drugs to men who are not actually candidates for the treatment.
- Dangerous side effects of this hormone therapy, including cardiac events 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 this limitation, testosterone prescriptions doubled in just four years between 2008 and 2012 largely because of aggressive advertisements from testosterone makers that directly targeted men.[3]

However, because of off-label marketing, many men without low T levels have received testosterone-replacement therapy 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 testosterone level.

Even worse, once testosterone therapy is initiated, patients may not be able to stop taking the drug. "Once you start, your body begins shutting down natural production of the hormone, thinking it's no longer needed," said Dr. Gregory Broderick.[4] An article in Men's Journal in 2011 reached the same conclusion.[5]

A McClatchy News report suggested that the marketing of AndroGel was positioned to make the treatment "ride (the) coat tails of Viagra."[6] But unlike Viagra, AndroGel was never approved by the FDA 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, the manufacturer of AndroGel[7] wanted to boost its sales with an aggressive strategy to push "off-label" uses of the drug. As a result, AndroGel has gained about 50 percent market share.

Researchers who have expressed concern over the off-label prescription of testosterone therapy gels note 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]

From 2000 to 2011, annual prescriptions for testosterone in the United States increased by a factor of five, to 5.3 million.

A pair of articles in JAMA Internal Medicine last August drew attention to the efforts to market testosterone therapy and discussed the strategy of "creating a crisis." The articles suggested that promotional campaigns for testosterone therapy are disguised as objective papers by physicians but are actually paid for by drug companies, then edited or even distorted to fit the company's agenda. Low T "disease," they said, 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 has used 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 that recommended the treatment and appeared to be objective scientific articles but that 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]

TESTOSTERONE THERAPY AND THE INCREASED RISK OF HEART ATTACK

Following the aggressive, off-label marketing of testosterone and recent studies linking testosterone gel 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," an FDA statement said.

A study published Jan. 29 by the Public Library of Science journal PLOS One[14] and led by William D. Finkle showed that, as compared with men who did not receive testosterone, men 65 years of age or older had double the risk of heart attack within 90 days after taking a testosterone gel. Among men younger than 65 years of age who had had a previous heart attack, the risk of a subsequent heart attack within 90 days after beginning to receive testosterone gels almost tripled.

Finkle said his research was prompted by a 2010 study in the New England Journal of Medicine that involved a clinical trial of testosterone gel in men older than 65 years of age. That study was halted after there was an increase in heart attacks and other heart issues in the group of participants who were receiving the testosterone-replacement gel.

In their PLOS One study, Finkle's group briefly addressed the research that preceded their own research 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 also showed that testosterone therapy was associated with a substantially increased risk of heart attack and stroke among men older than 65 years of age. The JAMA study involved more than 8,700 men who received treatment in Veterans Administration facilities and who had a total testosterone level of less than 300 ng per deciliter.[16]

More than 1,200 patients in the JAMA study received testosterone therapy. Nearly 20 percent of the men who did not receive testosterone therapy died or had heart attacks or strokes. However, 25.7 percent of the men who received testosterone supplements died or had heart attacks or strokes — an increased risk factor of nearly 30 percent.[17]

AFFECTED LABELS

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

- Androderm
- Axiron
- Bio-T-Gel
- Delatestryl
- Fortesta
- Striant
- Testim

Studies published in 2013 and 2014 suggested that testosterone gels might double — or even triple — the risk of heart attack among some men.

The Judicial Panel on Multidistrict Litigation recently created a centralized proceeding for testosterone-replacement therapy suits in the U.S. District Court for the Northern District of Illinois.

'HORMONE REPLACEMENT FOR MEN'

In its early stages, testosterone therapy litigation is similar to the hormone-replacement therapy 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), a drug (or therapy or treatment) has become popular among the general public.

Once a substantial number of patients begin using a treatment, research studies are conducted to test its 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 hormone-replacement therapy litigation was substantial. Pfizer alone was named in more than 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 who alleged that their cancer was caused by HRT.[18] The HRT litigation was based, in part, on an in-depth study published in JAMA in 2010 which showed that women using HRTs had an increased risk of breast cancer. This study involved 12,000 women over 11 years.[19]

As with 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 the natural hormones estrogen and progesterone. The hypothalamus 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. At 35 years of age or earlier, a woman's hormone production decreases considerably, beginning with a loss of progesterone. The level of progesterone decreases 120 times more rapidly than estrogen.

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

HRT refers to either the use of the combination of conjugated estrogens (estrogen) and progesterone (progestin) or the use of estrogen alone. A focus of HRT litigation has been the combined 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 that was published in JAMA. This article claimed that taking estrogen during menopause reduces the risk of breast and genital cancers. In his popular book "Feminine Forever," Wilson later claimed that menopause did not need to be a natural stage of life; what he did not divulge was that his research and writing were bankrolled by Wyeth.[20]

Wyeth created a demand for Premarin (and later Prempro) by over-promotion and aggressive marketing, particularly for off-label uses. Wilson, who characterized menopause as a disease rather than a phase of life, said that estrogen was the cure for "the tragedy of women." Menopause, he declared in his book, caused women to lose their youthful appearance and 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 rather a new disease.

Like some testosterone manufacturers, in its HRT campaign, Wyeth engaged a ghostwriting agency, DesignWrite, to promote HRT for women through medical journals. In both HRT and testosterone marketing, the goal was to publish widely with the appearance of objectivity and independence and to allay patient fears. According to a 2010 PLOS article:

> Between 1997 and 2003, DesignWrite's output for Wyeth on the Premarin family of products included "over 50 peer-reviewed publications, more than 50 scientific 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."

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.[22]

CONCLUSION

The recent studies published in JAMA and PLOS One have identified a serious scientific link between testosterone therapy gels and cardiac events, including heart attack and stroke. A number of lawsuits have already been filed, though this is probably just the beginning. Like the earlier HRT litigation, the testosterone litigation has focused on the manufacturers' aggressive, off-label marketing and undisclosed side effects.

Early complaints filed in February 2014 assert that Abbott and its AbbVie division "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."[23] As the market for these products grows, a number of complaints will probably be filed alleging cardiac injuries after the use of testosterone therapy.

(Editor's note: On June 6 the Judicial Panel on Multidistrict Litigation created a centralized pretrial proceeding for 45 testosterone-replacement therapy suits in the U.S. District Court for the Northern District of Illinois, In re Testosterone Replacement Therapy Products Liability Litigation, *MDL No. 2545.)*

NOTES

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[3] Jonathan LaPook, *Testosterone Supplements Linked to Heart Attacks in New Study,* CBS News, Jan. 29, 2014, *available at* http://www.cbsnews.com/news/testosterone-supplements-linked-to-heart-attacks-in-new-study/.

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

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

[6] *See* Adams, *supra* note 1.

[7] AndroGel has been through a number of corporate owners in the past 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.

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[11] Stephen R. Braun, *Promoting "Low T": A Medical Writer's Perspective,* 173 JAMA Internal Medicine 1458 (Aug. 12/26, 2013), *available at* http://archinte.jamanetwork.com/article.aspx?articleID=1726983.

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[13] *Id.*

[14] William D. Finkle, Sander Greenland, Gregory K. Ridgeway, John L. Adams, Melissa A. Frasco, Michael B. Cook, Joseph F. Fraumeni Jr. & Robert N. Hoover, *Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men,* 9 PLoS ONE (Jan. 29, 2014), *available at* http://www.plosone.org/article/info:doi/10.1371/journal.pone.0085805.

[15] *Id.* at 4-5.

[16] Rebecca Vigen, Colin I. O'Donnell, Anna E. Barón, Gary K. Grunwald, Thomas M. Maddox, Steven M. Bradley, Al Barqawi, Glenn Woning, Margaret E. Wierman, Mary E. Plomondon, John S. Rumsfeld & P. Michael Ho, *Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels,* 310 JAMA 1829 (Nov. 6, 2013), *available at* http://jama.jamanetwork.com/article.aspx?articleid=1764051.

[17] *Id.*

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

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[22] Adriane J. Fugh-Berman, *The Haunting of Medical Journals: How Ghostwriting Sold "HRT,"* 7 PLoS Med. (Sept. 7, 2010), *available at* http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000335.

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