

A summary of the controversy surrounding off-label medications in men's health

Adam Parker¹, Matthew Bruha¹, Oluwaseun Akinola², Charles Welliver^{1,3,4}

¹Albany Medical College, Albany, NY, USA; ²Royan Hospital, Lagos, Nigeria; ³Division of Urology, Albany Stratton Veterans Affairs Hospital, Albany, NY, USA; ⁴Urological Institute of Northeastern New York, Albany, NY, USA

Contributions: (I) Concept and design: M Bruha, C Welliver; (II) Administrative support: A Parker, M Bruha; (III) Provision of study materials or patients: A Parker, M Bruha, C Welliver; (IV) Collection and assembly of data: All authors; (v) Data analysis and interpretation: A Parker, O Akinola, C Welliver; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Charles Welliver, MD. Albany Medical College, 23 Hackett Boulevard, Albany, NY 12208, USA. Email: cwelliver@communitycare.com.

Abstract: While there are common and accepted practices in men's health, barriers exist to treatment of these disorders with Food and Drug Administration (FDA) approved medications. In male factor infertility, these barriers include studies that are often underpowered for desired outcomes. This has led to the use of medications previously examined in females in an off-label fashion for treatment of male infertility. Issues surrounding the treatment of hypogonadism in men are more complex, becoming increasingly so in the last few years. Drug companies have developed compounds for treatment of hypogonadism for particular subgroups of men. However, the indicated groups for these medications are narrow leading to these medications being regularly used for an indication the FDA considers to be part of "normal aging". This work will examine the controversy surrounding the use of off-label medications in men's health and how factors like pharma advertising, FDA regulation and difficulties in creating adequate studies has affected the current paradigm.

Keywords: Hormone replacement; controversy; off label; andrology

Submitted Jan 21, 2016. Accepted for publication Mar 06, 2016.

doi: 10.21037/tau.2016.03.07

View this article at: <http://dx.doi.org/10.21037/tau.2016.03.07>

Defining the label

The use of a medication in an "on-label" manner denotes that the medication in question has been approved by the U.S. Food and Drug Administration (FDA) for its considered use. Conversely, medication used in an "off-label" fashion means that use is not approved by the FDA for that particular disease or indication. Instead, the medication has likely been registered for a different use with the FDA after extensive study, or the medication is being dosed in a form and/or quantity not approved by the FDA (1). Use in this additional, non-label indication generally occurs when there are few to no options available in treatment for the disease in question, but there is a pathophysiologic basis wherein the mechanism of action of the off-label medication may potentially improve

patient outcomes. There is likely minimal evidence-based research on the disease process and no predominant class of medications that has an "on-label" indication for the condition being treated. Or, the physician may believe that using a given drug in an off-label fashion is a superior, safer option than a medication that has already been approved by the FDA as on-label for the given condition.

Differentiating between an on-label and off-label usage of a medication is important for multiple reasons. There are multiple and costly steps by which a medication is approved by the FDA. These steps involve trials with three phases in humans; the first phase evaluates safety and side effects, the second phase attempts to establish efficacy, and the third phase seeks to demonstrate efficacy beyond that of placebo in a larger variety of populations (2). While off-label use of a medication is allowed by the FDA under the correct

circumstances, substances used in this manner have not been studied for safety and efficacy in this additional patient population. It is important for many reasons that both the physician and patient be made aware of this distinction. Further, the FDA places responsibility on the physician to ensure that he or she is well informed about the product, is using firm scientific rationale, that sound medical evidence supports use of the medication in the manner being prescribed, and that he or she maintains records documenting such use (3). While the FDA is not involved in regulation of off-label medication use, the Supreme Court has commented that the acceptance and practice of off-label prescribing is a “necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine” (1,4).

While patients may frequently assume that all medications they are prescribed by physicians are FDA approved for the indication, this is very often not the case. Notably in the scope of this article, this assumption is seen in the use of selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). Frequent off-label use of medications has classically been seen in the treatment of male factor infertility but is now more commonly seen in the treatment of male hypogonadism.

The use of off-label medications in general is likely borne of several distinct problems. Drug registration trials are expensive, and the study of a new medication in a relatively small population (e.g., male infertility) may not be a cost effective venture for drug companies considering the number of medications that do not get approved following extensive testing. Additionally, even once medications pass approval, they can still be removed at a later date, as post-market assessment often discovers previously unrecognized adverse events. The implications of adverse events in vulnerable populations, particularly pregnant women or children, makes the search for new drug approval in these groups even less enticing to drug companies. In fact, it is thought that the majority of medications used in children may be for an off-label use (5).

Off-label medications in hypogonadism: a controversy is born

The exact mechanism linking aging to late onset hypogonadism remains unclear. Theories postulated include aging related hypothalamic-pituitary axis dysfunction. Although not proven in humans, experimentation in rodents show that apoptosis occurs in the aging hypothalamus

resulting in decreased production of gonadotropins (6). Alternatively, it has been suggested that aging is not the direct causative factor for late-onset hypogonadism (LOH) but instead the presence of age related co-morbidities (e.g., obesity, metabolic syndrome) (7,8).

Much of the FDA regulation regarding the use of testosterone therapy (TTh) in men with LOH applies to on-label use of testosterone products in patient populations for which therapy was not initially intended. Testosterone products have been approved as treatment by the FDA for replacement in men who “have low T (testosterone) levels due to disorders of the testicles, pituitary gland, or brain.” However, the FDA noted that testosterone products are “being used extensively in attempts to relieve symptoms in men who have low T for no apparent reason other than aging” (9). In that statement from March 2015, the FDA went on to state that “the benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man’s symptoms seem related to low testosterone.”

It is clear that the label intends for testosterone to be used in a more defined and small group than men getting TTh for LOH (10). That is, while there are certainly men who have this indication amongst those treated, the majority of men who are prescribed TTh more likely fall into the group of men who would be characterized as having age-related hypogonadism in the eyes of the FDA. Physicians should be careful to make this distinction with patients before initiating treatment, as LOH continues to be viewed as an off-label indication by the FDA. There are several safety trials ongoing that are well controlled and appropriately powered that may eventually soften the FDA stance (11,12).

Much of the controversy surrounding the use of TTh in men who have what is often referred to as LOH has been incited by the enormous resources drug companies have used to advertise to men for this off-label indication. The FDA’s official stance is clear on what is appropriate advertising for products, as a manufacturer is not permitted to promote a drug for other uses beyond the scope of what it was approved for (13). And yet, marked changes in sales of testosterone products, including gels, patches, injections, and tablets, have been observed recently. Prescriptions for testosterone products went up more than 50% between 2010 and 2012; total sales of testosterone products exceeded 2 billion dollars in 2012 (14). While there are undoubtedly a variety of age related changes (15-19) and medical co-morbidities that predispose men to the problem (20-25),

there has likely not been a large increase in the number of men who qualify in the relatively narrow on-label indication for treatment. Large increases in the number of testosterone prescriptions and overall revenue point to off-label use as a likely significant contributor.

A variety of potential causative factors for this increase in T-related revenue have been cited, with direct-to-patient marketing likely being an influencing factor, along with increased disease awareness (26). Over 100 million dollars were spent in the United States in 2012 to advertise the top brand-name T drugs—an amount that does not include unbranded campaigns, or advertising designed to raise awareness of low T (11). These campaigns are sponsored by T manufacturers, such as the website “IsItHypogonadism.com” (previously known as “IsItLowT.com”), but they are not generally regulated by the FDA because they are not officially treated as advertising. This is because these websites do not advertise directly; instead, they aim to raise low T awareness via various methods. One example of this non-advertising involves quizzes offered on the aforementioned website which are to be self-administered to prospective patients. These quizzes reference common, non-disease specific symptoms such as moodiness and increased body fat and link the potential cause of these symptoms to low testosterone. While it is possible that these non-descript symptoms are caused by low testosterone, it is unlikely if not impossible that low testosterone is the underlying cause in most cases. By raising awareness of low testosterone and attaching non-discriminatory symptoms to vague common problems, the use of unbranded campaigns has likely served to drive a large increase in testosterone prescriptions.

Beyond the issue of the appropriateness of on-label versus off-label use of TTh in older men is the question of whether TTh is advantageous to patients. The FDA has clearly stated the following: “for testosterone products for the testosterone replacement therapy (TRT) indication, the FDA-required efficacy testing is based upon pharmacokinetic assessments of serum testosterone concentrations and not based upon clinical efficacy parameters” (27). To clarify, the FDA’s standard in this case relies on whether the testosterone concentration is raised by TTh with little emphasis on improvements in either patient reported subject outcomes or objective measures beyond serum testosterone levels.

To answer this question, numerous authors have examined efficacy of TTh in men with LOH. Encouragingly,

men’s health researchers have found benefits in many outcomes that are important to patients. Improvements in sexual desire and function have been demonstrated with TTh (28-32). The regulatory effects of TTh on bone health (largely via aromatization to estrogens) has led to improvements in bone mineral density, with improvements in body composition and strength also seen (33-37). When looking at broader metrics, it appears that sufficient TTh may allow for increased longevity as well as a decrease in all-cause mortality (38,39). However, some studies have raised concerns about a link between TTh and an increased risk of heart attack or stroke, and further research has been recommended to clarify the risks of this treatment (40).

The use of off-label medications in male factor infertility

Infertility impacts approximately 6 million American couples (41). In roughly half the cases, a male factor is at least partially implicated, with half of these impacted men having been diagnosed with idiopathic infertility (42,43).

The paucity of a reliable medical treatment in male factor infertility is evident in a survey of American Urologic Association (AUA) members wherein many practitioners reported commonly using off-label drugs in the treatment of idiopathic male infertility (44). The authors found that two-thirds of urologists use medical treatments empirically in men with otherwise unexplained infertility. Clomiphene citrate, hCG and anastrozole were the most commonly used treatments. Surprisingly, 25% of respondents said they use exogenous testosterone, which significantly decreases sperm counts.

While many practitioners advocate the use of medical therapy for infertility, the effectiveness of the medications is still very much in question. The concept of empiric medical therapy for idiopathic male factor infertility was eloquently covered in a previous paper in this journal but is briefly summarized here (45). While some studies have demonstrated improvements in sperm counts and pregnancy rates, confirmatory studies have not yielded the same results (46-50). A Cochrane meta-analysis investigated ten randomized controlled studies utilizing either clomiphene citrate or tamoxifen for idiopathic oligo or asthenospermia (51). Authors found improved endocrine outcomes in treated patients compared to placebo but no statistical difference in pregnancy rates.

Intracavernosal injections (ICI) for erectile dysfunction

The only ICI agent with FDA approval for erectile dysfunction is alprostadil (a PGE-1 inhibitor). It was approved to treat impotence caused by neurological, vascular or psychological dysfunction. The most common significant side effect associated with intracavernosal alprostadil use is penile pain. Use of alprostadil as part of a combination of medications in therapies such as trimix originated from attempts to improve efficacy via synergism while minimizing side effects of the individual components. The production of these combination agents require compounding pharmacies and the dose of individual components in the combination may vary.

Trimix contains alprostadil, papaverine (a non-specific phosphodiesterase inhibitor that blocks both the breakdown of cAMP and cGMP) and phentolamine (an alpha blocker). The major side-effect associated with intracavernosal papaverine is penile fibrosis while the side-effects of intracavernosal phentolamine are less clear given its rare use as a sole agent for intracavernosal injection.

Studies (52,53) comparing the efficacy of trimix to alprostadil suggest equivalent frequency and quality of erections. While a significant decrease in pain was noted with trimix in the Bechara *et al.* study, there was no significant difference in penile pain between patients on alprostadil and trimix in the Seyam *et al.* study. The use of these combination injections is likely to remain off-label due to expense of FDA required trials in this small patient population.

Conclusions

Hypogonadism is a real problem for many men, one that can potentially be improved via focused medical attention. The use of off-label treatments such as TTh has been beneficial for men with LOH in several facets of health but continues to be controversial. In recent years, prescriptions and sales of T have increased dramatically, likely in large part due to off-label use and both direct and indirect marketing from manufacturers. Many of the aforementioned benefits of TTh have been implied via unbranded campaigns, such as informational websites, even though the benefits of TTh have not been correlated with men of all ages, men of all testosterone levels, etc.

To an extent, there is an inherent issue with the use of off-label medication, as by definition the rigors of testing

to achieve on-label status have not been completed. The physician should be aware of the uses and limitations of a treatment, and the patient should be made aware as well. In the case of TTh, further research is needed (and is ongoing) in to the appropriate cohorts for treatment as well as the potential side effects for different patient populations. The use of off-label medications for infertility and ICI for erectile dysfunction will most likely continue due to the costs associated with obtaining FDA approval in these small patient populations.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Committee on Drugs. American Academy of Pediatrics. Uses of drugs not described in the package insert (off-label uses). *Pediatrics* 2002;110:181-3.
2. U.S. Food and Drug Administration. The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective. Accessed Jan 17, 2016. Cited Jan 17, 2016. Available online: <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>
3. U.S. Food and Drug Administration. "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet. Accessed Jan 17, 2016. Cited Jan 17, 2016. Available online: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>
4. US Supreme Court. BUCKMAN CO. V. PLAINTIFFS' LEGAL COMM. (98-1768) 531 U.S. 341 (2001). Accessed Jan 17, 2016. Available online: www.law.cornell.edu/supct/html/98-1768.ZO.html
5. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. *Arch Pediatr Adolesc Med* 2007;161:282-90.
6. Morales A, Heaton JP. Hypogonadism and erectile dysfunction: pathophysiological observations and therapeutic outcomes. *BJU Int* 2003;92:896-9.
7. Sartorius G, Spasevska S, Idan A, et al. Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: the healthy man

- study. *Clin Endocrinol (Oxf)* 2012;77:755-63.
8. Corona G, Maggi M. Perspective: Regulatory Agencies' Changes to Testosterone Product Labeling. *J Sex Med* 2015;12:1690-3.
 9. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. Accessed Mar 3, 2016. Cited Jan 17, 2016. Available online: <http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm>
 10. U.S. Food and Drug Administration. AndroGel (testosterone) gel label. 2013. Available online: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021015s036lbl.pdf
 11. Snyder PJ, Ellenberg SS, Cunningham GR, et al. The Testosterone Trials: Seven coordinated trials of testosterone treatment in elderly men. *Clin Trials* 2014;11:362-75.
 12. Cauley JA, Fluharty L, Ellenberg SS, et al. Recruitment and Screening for the Testosterone Trials. *J Gerontol A Biol Sci Med Sci* 2015;70:1105-11.
 13. Henning JP. F.D.A.'s 'Off-Label' Drug Policy Leads to Free-Speech Fight. *The New York Times*, Aug 10, 2015, White Collar Watch.
 14. Singer Natasha. Selling That New-Man Feeling. *The New York Times*. Nov 23, 2013, BUSINESS DAY.
 15. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab* 2008;93:2737-45.
 16. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab* 2001;86:724-31.
 17. Kaler LW, Neaves WB. Attrition of the human Leydig cell population with advancing age. *Anat Rec* 1978;192:513-8.
 18. Neaves WB, Johnson L, Porter JC, et al. Leydig cell numbers, daily sperm production, and serum gonadotropin levels in aging men. *J Clin Endocrinol Metab* 1984;59:756-63.
 19. Rubens R, Dhont M, Vermeulen A. Further studies on Leydig cell function in old age. *J Clin Endocrinol Metab* 1974;39:40-5.
 20. Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* 2004;89:5462-8.
 21. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010;33:1186-92.
 22. Corona G, Monami M, Rastrelli G, et al. Type 2 diabetes mellitus and testosterone: a meta-analysis study. *Int J Androl* 2011;34:528-40.
 23. Glass AR, Swerdloff RS, Bray GA, et al. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. *J Clin Endocrinol Metab* 1977;45:1211-9.
 24. Zumoff B, Strain GW, Miller LK, et al. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. *J Clin Endocrinol Metab* 1990;71:929-31.
 25. Hofstra J, Loves S, van Wageningen B, et al. High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment. *Neth J Med* 2008;66:103-9.
 26. Baillargeon J, Urban RJ, Ottenbacher KJ, et al. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med* 2013;173:1465-6.
 27. Testosterone Replacement Therapy. Joint Meeting for Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSARM AC). College Park Marriott Hotel and Conference Center, Hyattsville, Maryland. Sep 17, 2014. Available online: <http://www.fda.gov/downloads/AdvisoryCommittee/.../UCM412537.pdf>
 28. Buvat J, Montorsi F, Maggi M, et al. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J Sex Med* 2011;8:284-93.
 29. Mikhail N. Does testosterone have a role in erectile function? *Am J Med* 2006;119:373-82.
 30. Bhasin S, Taylor WE, Singh R, et al. The mechanisms of androgen effects on body composition: mesenchymal pluripotent cell as the target of androgen action. *J Gerontol A Biol Sci Med Sci* 2003;58:M1103-10.
 31. Sinha-Hikim I, Cornford M, Gaytan H, et al. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. *J Clin Endocrinol Metab* 2006;91:3024-33.
 32. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of Testosterone Treatment in Older Men. *N Engl J Med* 2016;374:611-24.
 33. Bhasin S. Testosterone supplementation for aging-associated sarcopenia. *J Gerontol A Biol Sci Med Sci* 2003;58:1002-8.
 34. Kenny AM, Bellantonio S, Gruman CA, et al. Effects of

- transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2002;57:M321-5.
35. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: a review. *Maturitas* 2011;69:322-37.
 36. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536-59.
 37. Davey RA, Morris HA. Effects of estradiol and dihydrotestosterone on osteoblast gene expression in osteopenic ovariectomized rats. *J Bone Miner Metab* 2005;23:212-8.
 38. Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;97:2050-8.
 39. Muraleedharan V, Marsh H, Kapoor D, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169:725-33.
 40. Weintraub A. Safety Concerns Slow Sales of Testosterone Therapy. *Bloomberg Businessweek*, Nov 06, 2014.
 41. Quallich S. Examining male infertility. *Urol Nurs* 2006;26:277-88; quiz 289.
 42. Singh K, Jaiswal D. Human male infertility: a complex multifactorial phenotype. *Reprod Sci* 2011;18:418-25.
 43. de Kretser DM. Male infertility. *Lancet* 1997;349:787-90.
 44. Ko EY, Siddiqi K, Brannigan RE, et al. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. *J Urol* 2012;187:973-8.
 45. Dabaja AA, Schlegel PN. Medical treatment of male infertility. *Transl Androl Urol* 2014;3:9-16.
 46. Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial. *Fertil Steril* 2010;93:2232-5.
 47. Wang C, Chan CW, Wong KK, et al. Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia. *Fertil Steril* 1983;40:358-65.
 48. Hussein A, Ozgok Y, Ross L, et al. Clomiphene administration for cases of nonobstructive azoospermia: a multicenter study. *J Androl* 2005;26:787-91; discussion 792-3.
 49. Ghanem H, Shamloul R. An evidence-based perspective to the medical treatment of male infertility: a short review. *Urol Int* 2009;82:125-9.
 50. Check JH, Chase JS, Nowroozi K, et al. Empirical therapy of the male with clomiphene in couples with unexplained infertility. *Int J Fertil* 1989;34:120-2.
 51. Vandekerckhove P, Lilford R, Vail A, et al. Clomiphene or tamoxifen for idiopathic oligo/asthenospermia. *Cochrane Database Syst Rev* 2000;(2):CD000151.
 52. Bechara A, Casabé A, Chéliz G, et al. Prostaglandin E1 versus mixture of prostaglandin E1, papaverine and phentolamine in nonresponders to high papaverine plus phentolamine doses. *J Urol* 1996;155:913-4.
 53. Seyam R, Mohamed K, Akhras AA, et al. A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E1. *Int J Impot Res* 2005;17:346-53.

Cite this article as: Parker A, Bruha M, Akinola O, Welliver C. A summary of the controversy surrounding off-label medications in men's health. *Transl Androl Urol* 2016;5(2):201-206. doi: 10.21037/tau.2016.03.07