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The potential use of SERMS for the treatment of Andropause

Over the last decade, prescription sales of testosterone therapy products have soared more than 500 percent (Rhoden, 2004). The main drug sales has been Androgel, which, as the name implies, is a testosterone gel that is applied to the skin usually on the upper body. Prior testosterone replacement products where injectable and were not widely accepted. Some of the drawbacks to injection were the pain of the injections themselves and the spiky pattern of resulting testosterone levels, with higher-than average levels shortly after injection and a 2-3 week tapering off to below-average levels just prior to the next injection. Androgel became popular because it is easily applied and provides relatively stable levels throughout the day. There are, however, some little known potential side effects with Androgel (and other testosterone products) including reduced sperm count, softening and decreased size of the testicles and, occasionally, gynecomastia. The reasons for these less talked about side effects are simple: exogenous testosterone shuts off testicular production of endogenous testosterone, effectively decreasing sperm counts and testicular consistency. The hypothalamic-pituitary-gonadal axis senses the increased levels of exogenous testosterone and shuts off LH and FSH secretion thereby decreasing dramatically the testicles' own endogenous production of testosterone and sperm.

Since the majority of men on Androgel or other testosterone products are using it for treatment of symptoms related to andropause, these men usually have low testosterone levels related to secondary causes manifesting as a relative decreased LH response (otherwise known as secondary hypogonadism where the pituitary response to a decreased testosterone level is diminished). In these men exogenous testosterone makes the situation worse by further shutting down pituitary LH secretion. Gynecomastia is sometimes experienced because testosterone is normally broken down (aromatized) in fat tissue to estrogen. High levels of exogenous testosterone can, therefore, result in abnormally high estrogen levels, which, in turn, can stimulate growth of male breast tissue.

The original approved indication for Androgel was hypogonadism related to specific causes of testicular failure, but the majority of current sales appear to be for indications such as andropause. Andropause is probably best defined as symptomatic hypogonadism in adult men. Symptoms of andropause include decreased libido and erectile dysfunction, loss of muscle mass and strength, weight gain, and declining cognitive function. Hypogonadism is also associated with type II diabetes, insulin resistence, central obesity and the metabolic syndrome. Current scientific data are still preliminary and somewhat contradictory, but suggest a positive response to the symptoms of hypogonadism in adult men with testosterone therapy. Caution, however, is warranted. As we know, testosterone is strongly correlated with prostatic tissue growth, which is why all forms of testosterone are contraindicated in men with prostate cancer. Since prostate cancer is

slow growing and often undetected, many men may be increasing their risk for cancer by using testosterone products. This area of concern has received a lot of attention but, because the requisite studies can take years to conduct and evaluate, final recommendations regarding the connections between prostate cancer initiation and testosterone therapy may also be years in coming. In the meantime, all men using testosterone products should have initial and annual screenings for prostate-specific antigen (PSA) to help minimize the risk for cancer.

Selective estrogen receptor modulators (SERMS) are drugs that compete for the estrogen receptor and decrease the effects of estrogens on cells with those receptors. These drugs are informally called antiestrogens, and the category includes drugs such as Clomiphene, tamoxifene and toremiphene (chlorinated tamoxifene). Recent studies using these drugs to boost testosterone levels by stimulating the body's own endogenous production of testosterone are encouraging, and these drugs may ultimately prove to be a safer and more effective treatment for symptoms of andropause than exogenous testosterone replacement with Androgel or testosterone products. The potential benefits of antiestrogens are that endogenous production of testosterone does *not* result in sperm count decline, testicular changes or gynecomastia. These drugs also have the benefit of oral administration, which is far preferable by patients than either injections or gels.

A study titled "Chronic clomiphene citrate administration for the treatment of progressive hypogonadism in the aging male" presented at the 2003 AUA meeting by Shabsigh and colleagues showed that 25mg of Clomiphene citrate increased testosterone levels two fold in hypogonadal men within one month (610 $\pm$178 post treatment versus 248$\pm$40 at baseline). Interestingly the testosterone/estrogen ratio declined 40% as well. Guay et. al., (2003), showed similar increases in testosterone levels using clomiphene citrate and also showed that sexual function improved in 75% of the men studied. In addition, a study titled " Androxal for the treatment of hypogonadal men" presented by Wiehle and colleages at the International Congress of Endocrinology in September 2004, showed similar results with Enclomid (the active isomer of clomiphene citrate, cis-clomiphene). Testosterone levels increased approximately 75% within two weeks on a dose of 25mg. Interestingly in comparison to Androgel, DHT levels remained within the normal range for enclomid while the Androgel men had levels of DHT above the normal range. Maybe the most interesting and most encouraging study was by Steiner and Pound (2003). These researches found a 50% increase in both total and free testosterone by day 120 in men receiving 60mg/day of toremiphene. In the men studied there was a significant reduction in the frequency of prostatic intraepithelial neoplasm (PIN) detection. Of the men with PIN receiving Toremiphene more than half had a reduction in detection of PIN at rebiopsy 120 days later. The conclusion of this preliminary paper points to an antiprostate activity that might be beneficial in the treatment of men with PIN.

Overall, the data strongly suggest that SERM's may be useful in elevating serum testosterone levels in hypogonadal men. Whether these increases relate to improvement of symptoms has yet to be definitively proven, but research on this topic is underway.

Compared to available preparations of testosterone replacement medications, SERMs appear to have fewer potential side effects and are most likely more prostate "friendly" than current testosterone replacement products. We are in the midst of a tremendous boom in the treatment of hypogonadal men—a boom which entails a significant risk with existing preparations. Newer medications such as SERMs appear to have great potential and fewer risks, but results of larger late-phase clinical trials are necessary before final recommendations can be made.

References:

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