

## ENDOCRINOLOGY

# The Utilization and Impact of Aromatase Inhibitor Therapy in Men With Elevated Estradiol Levels on Testosterone Therapy



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## ABSTRACT

**Introduction:** Testosterone therapy (TTH) for testosterone deficiency (TD) may lead to elevated estradiol (E2) levels requiring management to avoid unnecessary adverse effects.

**Aim:** To examine the impact of aromatase inhibitors, specifically anastrozole (AZ), in men with elevated E2 on TTH.

**Methods:** All patients on TTH at a high volume sexual medicine practice between 2005 and 2019 were reviewed. Men with E2 levels >60 pg/mL regardless of symptoms or 40–60 pg/mL with subjective symptoms were started on AZ 0.5 mg 3x/week. Routine hormone profile and symptom assessment were completed to ensure symptom resolution, reduction of E2 levels and maintenance of testosterone levels. Multivariable logistic regression was completed to determine predictors of men more likely to respond to therapy.

**Main Outcome Measure:** Demographic and hormonal profiles of men on AZ and predictors of response to therapy.

**Results:** 1708 men with TD were placed on TTH. Of these, 51 (3%) were treated with AZ (AZ+). After exclusions, 44 (2.6%) had elevated estradiol levels >60 pg/mL or >40 pg/mL with symptoms. Demographics were similar between groups. TTH distribution between groups was different with greater rates of topical TTH in the AZ- groups (AZ+:34.1% vs AZ-:53.5%) and greater rates of intramuscular TTH in the AZ+ group (AZ+:38.6% vs AZ-:18.5%) ( $P = .017$  overall). Of the 44 men treated with AZ, 68.0% had pre-AZ E2 levels  $\geq 60$  pg/mL and 32.0% had levels between 40 and 60 pg/mL. Median pre-AZ E2 levels were 65 (interquartile range [IQR], 55–94) pg/mL in comparison to 22 (IQR 15–38) pg/mL post-AZ E2 levels ( $P < .001$ ). Total testosterone levels were similar before and after AZ use (616 (IQR 548–846) ng/dL and 596 (IQR 419–798) ng/dL, respectively,  $P = .926$ ). No statistically significant predictive factors of E2 reduction using AZ were found.

**Conclusion:** While no statistically significant predictors for E2 recovery in men on AZ were found, AZ remains a reasonable option for E2 reduction in men with elevated levels on TTH. **Punjani N, Bernie H, Salter C, et al. The Utilization and Impact of Aromatase Inhibitor Therapy in Men With Elevated Estradiol Levels on Testosterone Therapy. Sex Med 2021;XX:XXXXXX.**

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**Key Words:** Testosterone; Anastrozole; Estradiol; Aromatase Inhibitor

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## INTRODUCTION

Testosterone deficiency (TD) occurs in 6–25% of men.<sup>1,2</sup> As per the American Urological Association guidelines, treatment of low testosterone (T) is indicated if the levels are below the threshold of 300 ng/dL with associated signs or symptoms.<sup>2</sup> TTH may increase estradiol (E2) levels via aromatase enzyme activity (aromatization), which converts T to E2.<sup>3</sup> Anastrozole (AZ) is an aromatase inhibitor which targets aromatase preventing conversion.<sup>4</sup>

In general, AZ is indicated to delay epiphyseal maturation in adolescent boys but has been used in the infertile male with TD

and elevated E2 levels to preserve spermatogenesis.<sup>4</sup> The AZ side effect profile has been studied extensively in women and is well-tolerated medication.<sup>4</sup> Elevated E2 level is most commonly associated with gynecomastia, but is not the only responsible mechanism.<sup>5</sup> AZ has been used to treat men with elevated E2, but currently limited evidence and/or guidelines exist for the optimal management of elevated E2 levels in men on TTH.

Given this we specifically explore if our proposed management strategy for elevated E2 levels with AZ was effective in reducing E2 levels while maintaining appropriate T levels and if we could determine any predictors of those most likely to respond?

## METHODS

**Study Population:** Data were retrospectively reviewed for all TD men at a single center high volume sexual medicine practice between 2005 and 2019. Men were considered to have TD if they had documented T levels <300 ng/dL on two separate occasions with associated signs or symptoms. In the absence of guidelines for the use of AZ in men TD men with elevated E, men with either E2 levels >60 pg/mL or 40–60 pg/mL with subjective symptoms (ie, breast or nipple tenderness) were started on anastrozole 0.5mg three times per week (off-label). Men were excluded if they were started on AZ from an external physician as baseline estradiol levels were unknown, or if they had breast cancer. Demographic comorbidity, and TTH modality data were recorded. Study approval was obtained from the Institutional Review Board at Memorial Sloan Kettering Cancer Center (IRB 16-1526).

**Laboratory Assessment and Titration:** T levels were assessed using liquid chromatography mass spectrometry (LCMS) (50% pre-AZ and 57% post-AZ) and were completed before 10 AM. E2 levels were assessed similarly by LCMS each time T levels were measured by LCMS. Free T and luteinizing hormone (LH) were also measured. E2 levels were titrated between 20 and 40 pg/mL through either modulation of frequency and/or dosage of AZ. Hormone levels were recorded before (baseline) and after AZ commencement.

**Statistical Analysis:** Demographic data and groups were compared using t-test and chi-square tests. Pre- and postanastrozole hormone levels were compared using Wilcoxon rank sum to assess differences in pairwise means. Logistic regression was used to determine predictive factors for those more likely to respond to anastrozole treatment defined as a composite score (both reduction of estradiol to less than 60 pg/mL and a 20 pg/mL decrease in estradiol levels). All analysis was completed using Stata/IC v16 (StataCorp, College town, TX).

## RESULTS

**Study Population:** Of 1708 men with TD placed on TTH, 51 (3%) were treated with AZ (AZ+). Of these, 7 (14%) were excluded (3 previously on AZ and 4 with breast cancer history). A total of 44 (2.6%) exhibited elevated estradiol levels (range 40–165 pg/mL) and were included. The median time on TTH

**Table 1.** Multivariable analysis of predictors of E2 normalization\*

In response to anastrozole	Odds Ratio (95% CI)	P value
<i>Demographics</i>		
Age (per decade)	0.98 (0.48–2.03)	.963
Comorbidity** (any vs. none)	0.66 (0.09–4.79)	.678
<i>Testosterone therapy</i>		
Topical	Ref	Ref
Clomiphene	0.08 (0.01–1.30)	.076
IMT	0.18 (0.01–2.45)	.200

\*Estradiol levels from 60 pg/mL to <60 pg/mL plus ≥20 pg/mL decrease while on anastrozole.

\*\*One or more of the following: hypertension, hyperlipidemia, obstructive sleep apnea, diabetes mellitus.

prior to initiation of AZ was 11.96 months (IQR 4.63–31.44). The remaining 1657 men (97.0%) did not receive AZ treatment (AZ-). Median age and BMI of groups were comparable (Supplementary Table 1). The majority of men in both groups were never-smokers (AZ+ 54.5%, AZ- 43.1%), and more men in the AZ+ group had obstructive sleep apnea (OSA) (AZ+ 22.7%, AZ- 12.8%,  $P = .055$ ). More men utilized topical TTH treatment in the AZ- group (53.5%) compared to AZ+ group (34.1%), and more intramuscular TTH usage in the AZ+ (38.6%) compared to AZ- group (18.5%) ( $P = .017$  overall).

**Laboratory Data:** Of the men on AZ, median pre-AZ E2 levels, were 65 (interquartile range [IQR], 55–94) pg/mL in comparison to 22 (IQR 15–38) pg/mL post-AZ treatment ( $P < .001$ , Supplementary Table 2). The median time on AZ at the time of E2 assessment was 1.98 months (IQR 0.64–6.88). Total T levels were similar before and after AZ use (616 (IQR 548–846) ng/dL and 596 (IQR 419–798) ng/dL, respectively,  $P = .926$ ). Free T and LH levels were similar pre- and post-AZ use ( $P = .922$ ,  $P = .861$ , respectively). Of the 44 men treated with AZ, 68.0% had pre-AZ E2 levels ≥60 pg/mL and 32.0% had levels between 40 and 60 pg/mL.

**Estradiol Recovery Predictors:** On multivariable analysis (Table 1), age per decade, the presence of at least one comorbidity (hypertension, hyperlipidemia, sleep apnea or diabetes) or type of TTH were not predictive of E2 normalization using AZ using a composite definition of estradiol response.

## DISCUSSION

Men receiving exogenous TTH may experience side effects, including elevations in E2 levels, which may impact libido and cause gynecomastia. AZ is a safe and effective option for men with elevated E2. Our study evaluated men with TD in which a small subset had elevated E2 requiring intervention (AZ). Overall, we demonstrated a statistically significant reduction in E2 levels to normal physiologic levels with maintenance of T levels, but were unable to identify predictors for men most likely to respond to therapy.

Only 2.6% of men had E2 which warranted treatment with AZ. AZ has been used in men with TD in an effort to reduce the

conversion to E2 to T while maintaining fertility.<sup>6</sup> We employed a cut-off for the use of AZ, but the literature does not support a clear cut-off or indication for the initiation of estradiol-lowering therapy.<sup>7</sup> Similar to our series, in a national sample, 3.5% (1,200/34,016) of men were placed on an AI.<sup>7</sup>

Men in our series receiving AZ, and therefore with higher E2, had greater rates, although not statically significant, of OSA. Obesity is a common risk factor for OSA, and men with obesity have increased physiologic levels of aromatase therefore increasing the conversion of T to E2.<sup>8</sup> However, while not statistically significant, BMI of the AZ+ group was greater than the AZ- group. Obese men on TTH for TD may warrant closer observation of E2 levels

AZ- in our series had statistically significant use of topical TTH, whereas AZ+ men had statistically significantly greater proportions of intramuscular TTH and lower topical TTH use. This reflects some data which suggested that statistically significant increases in E2 were observed in men on injectable therapy 3 months after initiating TTH.<sup>9</sup>

Almost all men had recovery of E2 within normal levels (<40 pg/mL) with simultaneous maintenance of a serum T. This highlights the importance of appropriate regulation given the important physiological processes regulated by E2.<sup>5</sup> While AZ is commonly used as an adjunctive therapy to increase T levels in men whom spermatogenic preservation is important and therefore avoidance of exogenous testosterone is crucial, in our series AIs did not impact testosterone levels. However, other studies suggest coadministration of an AI with exogenous TTH increases serum T.<sup>10</sup> All of these received T pellets, suggesting a differential response based on TTH type.

No statistically significant predictors were found in our series to predict E2 recovery in men on AZ. To the best of our knowledge, this has not been previously reported. Furthermore, limited data exists with respect to a clear cut-off or consideration of response to AZ, and therefore our composite cut-off was suggested based on a clinically meaningful response.

The clinical implications of AZ in men with elevated E2 while on TTH are evident. Given the importance of E2 in male physiology and the impact of TTH on E2, careful monitoring by practitioners providing exogenous therapy is critical.

Limitations to our study include the retrospective design, but all data were collected prospectively. The study does have limited external validity as data were obtained from a single institution and single provider. We also did not discern nor account for possible physiologic differences in men on AZ on clomiphene citrate versus those on exogenous TTH. We were not able to validate if AZ or clomiphene citrate did not interfere with E2 immunoassay testing. Furthermore all men did not have measurements completed by LCMS but were included in order to obtain a reasonable sample size. A sensitivity analysis only using LCMS measurements revealed similar results (Supplementary Table 3). Finally, while the number of men on AZ in our series is small

which limited statistical analysis for predictors of estradiol recovery, the total number of men assessed with TD was significant and over a large period of time.

## CONCLUSION

In patients with elevated E2 on TTH, using AZ 0.5mg TID, results in a statistically significant reduction in E2, with 76% completely normalized with simultaneous maintenance of T levels. No statistically significant predictors were found for recovery of E2 levels. Further research and larger studies are warranted.

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*Conflict of Interest:* The authors report no conflicts of interest.

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## STATEMENT OF AUTHORSHIP

Conceptualization - JM Investigation - HB, CS, JF, NB, JM; Formal Analysis - NP, JM; Writing Original - NP, JM; Writing Reviewing and Editing - NP, JM; Supervision - JM.

## REFERENCES

1. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007;92:4241-4247.
2. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol* 2018;200:423-432.
3. Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. *Indian J Urol* 2014;30:2-7.
4. de Ronde W, de Jong FH. Aromatase inhibitors in men: effects and therapeutic options. *Reprod Biol Endocrinol* 2011;9:93.
5. Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. *Asian J Androl* 2016;18:435-440.
6. DiGiorgio L, Sadeghi-Nejad H. Off label therapies for testosterone replacement. *Transl Androl Urol* 2016;5:844-849.
7. Tan RS, Cook KR, Reilly WG. High estrogen in men after injectable testosterone therapy: the low T experience. *Am J Mens Health* 2015;9:229-234.
8. Cohen PG. Obesity in men: the hypogonadal-estrogen receptor relationship and its effect on glucose homeostasis. *Med Hypotheses* 2008;70:358-360.
9. Pastuszak AW, Gomez LP, Scovell JM, et al. Comparison of the effects of testosterone gels, injections, and pellets on serum hormones, erythrocytosis, lipids, and prostate-specific antigen. *Sex Med* 2015;3:165-173.

10. Mechlin CW, Frankel J, McCullough A. Coadministration of anastrozole sustains therapeutic testosterone levels in hypogonadal men undergoing testosterone pellet insertion. *J Sex Med* 2014;11:254–261.

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.esxm.2021.100378>.