Coadministration of Anastrozole Sustains Therapeutic Testosterone Levels in Hypogonadal Men Undergoing Testosterone Pellet Insertion

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ABSTRACT

Introduction. Current U.S. Food and Drug Administration–approved therapies for hypogonadism involve testosterone (T) replacement. Testosterone pellets (TP) require a minor office procedure every 3 to 4 months. The need for repeated insertions increases the likelihood of a complication. Anastrozole (AZ) is an aromatase inhibitor that has been used off-label for the treatment of male hypogonadism. AZ increases T levels by lowering serum estradiol (E2) levels and increasing gonadotropin (GTP) levels.

Aim. We hypothesized that the concomitant use of AZ with TP insertions would sustain therapeutic T levels and increase the interval between TP insertions.

Methods. Men treated with TP for hypogonadism at an academic center were offered AZ (1 mg/day) at the time of TP reinsertion as a way of potentially decreasing the frequency of TP insertions. Total T (TT), free T (FT), sex hormone binding globulin, E2, luteinizing hormone (LH), and follicle-stimulating hormone FSH levels were obtained prior to T replacement and at 6 and 15 weeks from TP insertion. Men were re-implanted at 16 weeks if their TT levels were less than 350 ng/dL and their symptoms recurred. We retrospectively reviewed our records of men who underwent TP, TP, and AZ from 2011 to 2012. Demographics, TT, FT, LH, FSH, and E2 levels were recorded. Data were analyzed with ANOVA and a Tukey's test.

Main Outcome Measure. TT level at 6, 15, or >15 weeks from TP insertion.

Results. Thirty-eight men with 65 insertions were analyzed. The TP AZ group had significantly higher TT and FT levels than the TP group at >120 days ($P < 0.05$). The TP group had significantly higher E2 levels at all time points ($P < 0.01$). GTP levels remained stable in the TP AZ group. Average time to reinsertion in TP AZ was 198 days vs. 128 days in the TP group.

Conclusion. Men on TP AZ maintain therapeutic T levels longer than men on TP alone and have significantly less GTP suppression. **Mechlin CW, Frankel J, and McCullough A. Coadministration of anastrozole sustains therapeutic testosterone levels in hypogonadal men undergoing testosterone pellet insertion. J Sex Med 2014;11:254–261.**

Key Words. Testosterone Pellets; Aromatase Inhibitor; Hypogonadism; Testosterone Deficiency Syndrome

Introduction

The overall prevalence of symptomatic hypogonadism is 5.6% in men aged 30–79 years and in longitudinal studies increases 1.5–2% per year after age 40 [1]. Testosterone (T) deficiency is a lifelong problem. Endocrine guidelines recommend T replacement in symptomatic men to induce and maintain sexual function, a sense of well-being, muscle mass and strength, and bone mineral density [2]. All U.S. Food and Drug Administration (U.S. FDA)–approved treatment modalities involve T replacement with injections, transdermal gels or patches, buccal lozenges, or long-acting T pellets (TP).

TP were U.S. FDA approved in 1972 and are crystalline TP that are subcutaneously implanted and enter systemic circulation through diffusion

[3]. TP have a predictable decay curve, provide sustained therapeutic T levels, and may reduce noncompliance [4–7]. The average time to re-implantation is 3–4 months after which time T levels return to pretreatment values [5,7]. TP involve an office procedure with a small risk of bleeding, infection, pain at the implant site, and extrusion [5,7]. This treatment also is associated with suppression of gonadotropins (GTPs) [4]. Prolonged exogenous suppression of testicular function often leads to testicular atrophy. GTP suppression appears to be largely mediated through the peripheral and central aromatization of T to serum estradiol E2 that occurs with exogenous T supplementation [8,9].

The pituitary gland secretes luteinizing hormone (LH), which stimulates Leydig cells in the testes to secrete T [8]. GTP-releasing hormone stimulates the pituitary to release both LH and follicle-stimulating hormone (FSH). T and estrogen exert direct negative feedback at both the pituitary and hypothalamic level [8,10]. T is peripherally and centrally converted to E2 by aromatase [9]. E2 has a potent negative effect on T production and is the main regulator of FSH secretion [11,12]. The negative feedback of estrogens can either be blocked at the receptor level or by preventing the breakdown of T to estrogens by aromatase [8].

Aromatase inhibitors (AI) were U.S. FDA approved for use in women in 1996 and have been studied in infertile, obese, and elderly hypogonadal men. Two randomized double-blind placebo-controlled trials by Leder et al. showed a significant increase in T levels in elderly men on 1 mg of anastrozole (AZ) daily [13,14]. The average total T (TT) levels increased from 323–343 (mg/dL) to 525–572 at 3 months. Letrozole was prospectively studied in 27 infertile men at a dose of 2.5 mg daily for 6 months. The average T level increased from 255 to 527 by 3 months [15]. Similar results with letrozole were seen in a recent prospective study by Gregoriou et al. [16]. Raman and Schlegel retrospectively reviewed the efficacy of testolactone or AZ on T levels in 140 infertile men. Average T levels increased from 277 to 411 and 295 to 445 in the testolactone and AZ groups, respectively [17]. There is good evidence to show that AIs significantly increase T levels in men.

There are two previous studies that have investigated the use of AIs in combination with depot-testosterone supplementation. Both of these studies were performed in a select group of men with epilepsy. The initial retrospective study included 17 hypogonadal men treated with depot-T alone or with the steroidal AI testolactone [18]. Although bioactive T (BAT) levels were not different between groups the combination group had higher sexual function scores (Brief Sexual Function Score) and lower estrogen levels. In 2010, Herzog et al. reported the results of a randomized placebo-controlled trial (RPCT) in 37 hypogonadal epileptic men treated either with depot-T alone or in combination with AZ [19]. They found that normalization of sexual interest and function scores occurred with a greater frequency in the combination group. These men had higher T to estrogen ratios but BAT levels were not significantly different between groups.

To our knowledge combination therapy with AIs and long acting TPs has not been previously reported, nor has the use of AIs with exogenous T in men without epilepsy been reported. We hypothesized that adding AZ to TP treatment would prolong therapeutic T levels. This might decrease the frequency of reinsertion and the overall morbidity over a lifetime of TP insertions.

Methods

Starting in May 2011 symptomatic hypogonadal men (T < 350 ng/dL) previously treated with TP (TP group) in our clinic were offered AZ (1 mg PO daily)(manufactured by AstroZeneca in London, UK) in addition to TP (TP AZ group) at their reinsertion visit in an attempt to prolong therapeutic T levels (>350 ng/dL). Each men received 10 pellets (75 mg per pellet) (manufactured by Slate Pharmaceuticals, Durham, North Carolina, USA). TPs were inserted in a single track in the gluteal region with the patient in the prone position. Patients were counseled that AIs were not U.S. FDA approved for the treatment of male hypogonadism but have been found to be well tolerated and effective in increasing T levels in published studies. Their mechanism of action was explained, and patients were counseled regarding possible side effects including rashes, diarrhea, headaches, joint pain, and changes in liver function enzymes.

TT, free T (FT), LH, FSH, sex hormone binding globulin (SHBG), and E2 levels were routinely obtained prior to T replacement and then at approximately 6 weeks and 4 months from treatment. Reinsertion was predicated on T levels and symptoms of hypogonadism. After institutional review board approval records were

Table 1 Baseline characteristics

Group	TP	TP AZ	*P* value
Number of treatments	34	31	NS
Age (SD)	62 (11)	58 (7.5)	NS
BMI (SD)	31 (6.3)	32.5 (5.9)	NS
Primary diagnosis (% of total)			NS
Hypogonadism	53	51	
Erectile dysfunction	38	39	
Peyronie's disease	3	0	
Other	6	10	
Baseline labs			
Total testosterone in ng/mL (SD)	204 (83)	224 (89)	NS
LH in mIU/mL (SD)	5.2 (4.7)	3.2 (2.6)	NS
FSH in mIU/mL (SD)	5.9 (3.9)	5.5 (4.2	NS
Estradiol in pg/mL (SD)	33 (4)	39.9 (3.5)	NS

retrospectively reviewed. Men with GTPs elevated more than 2× normal were excluded from our analysis (four subjects in both the TP and TP AZ group). Demographics and hormone levels were recorded. Data were analyzed with ANOVA and Tukey's test.

Results

Data from 65 insertions in 38 men were analyzed. Twelve patients had both TP and AZ. Baseline characteristics were similar in both treatment groups (Table 1). The average age was 60 ± 9 and body mass index 32 ± 6. The most common presenting diagnosis was symptomatic hypogonadism (47%) followed by erectile dysfunction (30%). Baseline hormone levels were similar in both groups (Table 1).

Hormone levels in TP and TP AZ groups are shown in Table 2 and Figure 1. After 120 days of treatment TT, FT, and average change in T levels were significantly higher in the TP AZ than the TP group ($P < 0.01$). TP AZ had a trend toward higher total T levels at 0–60 days ($P = 0.06$) and FT levels were higher at this time point ($P < 0.01$). SHBG levels did not significantly change in either group.

E2 levels were significantly higher in the TP group at all time points. GTP levels were profoundly suppressed in the group receiving only TP (Table 2, Figure 2). GTP levels remained above the lower limit of normal in the TP AZ group. GTP levels did not decrease significantly at any of the time points in the TP AZ group and actually increased after 120 days. E2 increased as GTP decreased in the TP group (Figure 2).

The time to reinsertion for both groups is shown in Figure 3. Fifty treatments had sufficient data available to analyze the time to reinsertion. Fifteen treatments were excluded. Two subjects were lost to follow-up, three were noncompliant, nine started AZ monotherapy, and one started androgen ablation therapy for prostate cancer.

Table 2 Hormone levels in TP AZ and TP groups

		Days from treament			
	Baseline	0–60	61–120	121–180	Statistical significance
Total T in ng/mL (SD)					Total T
TP (n)	204 ± 83 (34)	590 ± 187 (26)	453 ± 117 (12)	287 ± 69 (10)	*$P < 0.05$, TP AZ > TP
TP AZ (n)	224 ± 89 (31)	700 ± 207 (21)	430 ± 172 (21)	*487 ± 136 (16)	
Change in total T in ng/mL (SD)					Change in total T
TP	n/a	378 ± 207 (26)	249 ± 121 (12)	59 ± 88 (10)	*$P < 0.001$, TP AZ > TP
TP AZ	n/a	468 ± 194 (21)	206 ± 149 (21)	*218 ± 154 (16)	
Free T in pg/mL (SD)					Free T
TP	6.9 ± 8.2 (29)	14.5 ± 4.8 (18)	10.4 ± 3.9 (12)	6.3 ± 1.8 (7)	*$P < 0.01$, TP AZ > TP
TP AZ	7.8 ± 9.1 (22)	*19.2 ± 6.1 (19)	12.4 ± 4.8 (20)	*10.8 ± 3.6 (14)	
SHBG in nmol/L (SD)					SHBG
TP	30.0 ± 11.1 (16)	28.2 ± 10.5 (21)	29.7 ± 18.2 (8)	33.1 ± 12.3 (4)	None.
TP AZ	30.2 ± 8.9 (13)	30 ± 11 (12)	27.3 ± 8.1 (13)	30.3 ± 12.1 (13)	
LH in mIU/mL (SD)					LH
TP	5.2 ± 4.7 (30)	0.8 ± 1.6 (22)	0.4 ± 0.5 (11)	2.6 ± 2.8 (9)	*$P < 0.05$, TP AZ > TP
TP AZ	3.2 ± 2.6 (19)	*3.0 ± 4.5 (19)	*3.6 ± 2.3 (20)	*5.6 ± 2.3 (14)	
FSH in mIU/mL (SD)					FSH
TP	5.9 ± 3.9 (32)	1.3 ± 2.1 (22)	1.8 ± 1.7 (12)	6.0 ± 9.8 (9)	*$P < 0.01$, TP AZ > TP
TP AZ	5.5 ± 4.2 (22)	*5.1 ± 4.9 (20)	*5.7 ± 3.1 (21)	8.6 ± 3.3 (16)	
Estradiol in pg/mL (SD)					Estradiol
TP	33 ± 4 (24)	*46.1 ± 18.5 (22)	*33.6 ± 18.1 (12)	*27.8 ± 9.4 (7)	*$P < 0.05$, TP > TP AZ
TP AZ	39.9 ± 3.5 (16)	18.3 ± 11.8 (18)	17.7 ± 11.5 (21)	15.6 ± 11.6 (16)	
T/E2 ratio (SD)					T/E2 Ratio
TP	7.1 ± 2.6 (23)	14.2 ± 5.6 (22)	19.4 ± 14.3 (12)	10.8 ± 7.5 (7)	*$P < 0.01$, TP AZ > TP
TP AZ	8.7 ± 4.2 (16)	*67.8 ± 59.7 (18)	42.6 ± 45.3 (21)	*42.4 ± 5.0 (16)	

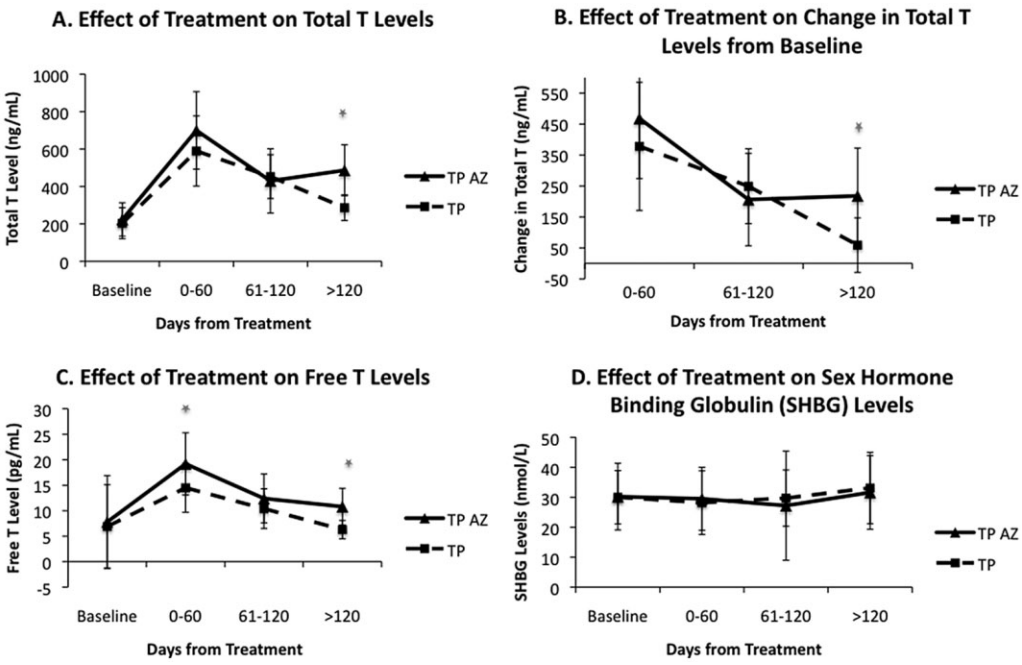

Figure 1 Total T, change in total T and free T were significantly higher for TP AZ compared with TP alone at >120 days (*$P < 0.01$) (A–C). There was no difference in SHBG levels (D). Error bars are standard deviations.

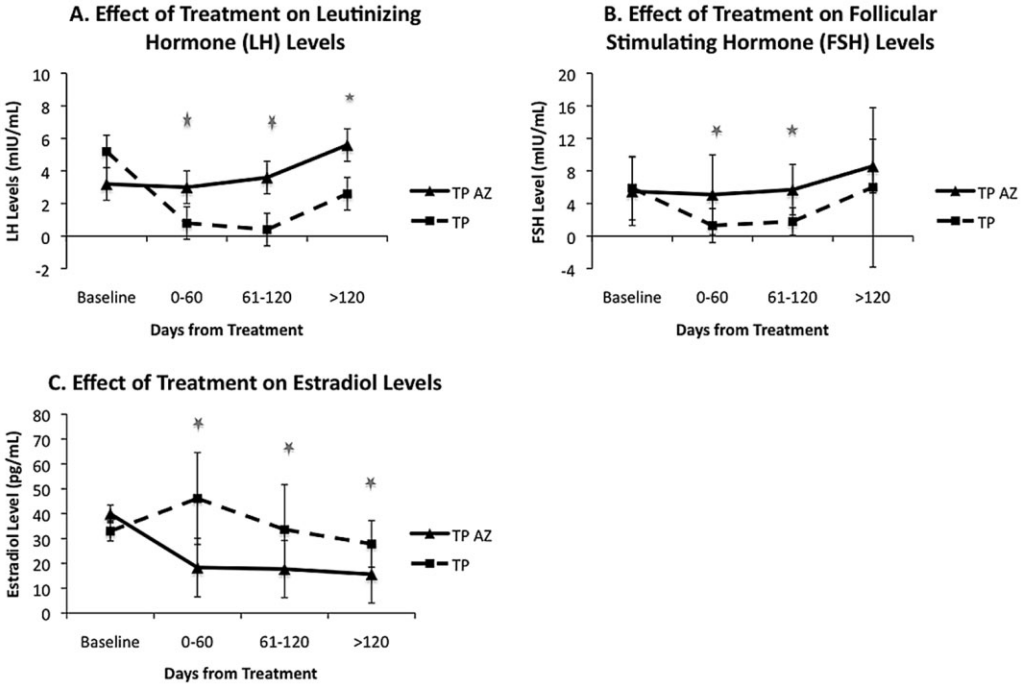

Figure 2 LH levels were significantly lower in the TP than the TP AZ group ($P < 0.01$) (A). FSH levels were significantly higher with anastrozole compared with TP alone ($P < 0.01$) (B). Estradiol levels were significantly higher in the TP group than TP AZ treatment at all time points ($P < 0.05$) (C).

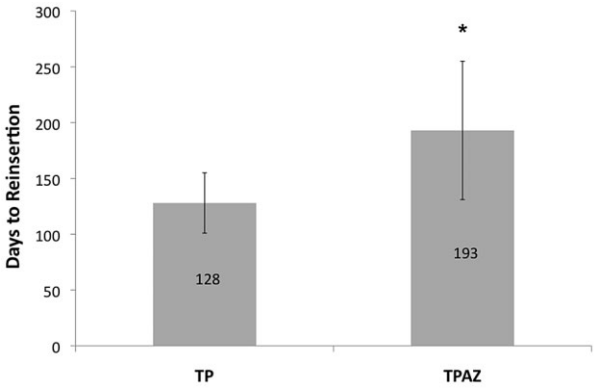

Figure 3 AZ increases time to reinsertion. (Error bars represent standard deviations.) (*$P < 0.01$)

The mean time to reinsertion was 124 days ± 22 days in TP (N = 23) and 193 ± 62 days in TP AZ (N = 27) ($P < 0.01$). Nine subjects (25%) in TP AZ did not undergo reinsertion at a mean f/u of 360 ± 141 days and were maintained on AZ.

Discussion

The maintenance of T homeostasis is a delicate balance between production and breakdown. The half-life of T is short, less than 60 minutes [20]. Over 90% of T is metabolized by hepatic dehydrogenases. Another 1% is converted to E2 by aromatase and 7% to dihydrotestosterone through alpha reductases [21,22]. T replacement strategies have to overcome the rapid first pass hepatic metabolism as endogenous production is virtually eliminated with replacement.

TP insertions are effective in treating hypogonadism and sustain T levels for 3–6 months as per package insert [10,23]. Repeated insertions can increase the risk of complications over a patients' lifetime. Exogenous T has been shown to cause GTP suppression in both long- and short-acting forms (gels, patches, intramuscular injections, and TP) [4,24,25]. E2 increases through aromatization of T during T replacement [24,26–28]. Aromatase has been demonstrated in the testes, brain [29,30], adipose tissue [9,31], muscle [32], hair [33], bone [34,35], and vascular tissue [36]. Eighty percent of circulating E2 is derived from peripheral aromatization of testicular or adrenal androgens. Increasing E2 suppresses GTP at the pituitary and hypothalamic level.

AZ is a generic competitive inhibitor of aromatase that converts T to E2. Pharmacokinetic studies of AZ in Korean males showed 90% bioavailability with very little intersubject variability. The peak serum concentration (1,500 ng/dL) was reached at 1 hour, and the half-life was 41 hours [37]. AZ has been used off-label primarily to treat male hypogonadal men with infertility [16,17,38]. It has also been used off-label to treat late onset hypogonadism [13,14]. AZ has been shown to raise T levels into the eugonadal range (>500 ng/dL), while increasing LH and FSH. The favorable pharmacokinetic characteristics of this drug make it an attractive alternative to T replacement therapy in men who are with an intact pituitary–gonadal axis.

We hypothesized that combining AZ with TP might decrease the peripheral conversion of exogenous T and prevent GTP suppression thereby maintaining endogenous T throughout the treatment and prolonging the therapeutic window of each implant. This is the first reported series on the concomitant use of AI with TP insertion.

We found that at a mean of 40 and 36 days TT and FT were comparable between groups, whereas LH and FSH were over 2.5-fold greater, and E2 levels were over twofold less in the TP AZ vs. TP group, respectively. The initial peak levels that we observed in both groups are comparable to levels reported in the literature for TP and are presumably due to the TP effect and the dissolution of the pellets. Despite the elevated T levels, GTPs were not suppressed in the TP AZ group. At a mean of 104 and 100 days TT and FT were comparable between TP AZ and TP, respectively. However, the significant disparity of the LH, FSH, and E2 levels persisted. After 120 days T and FT levels were significantly different, with no T values below 350 ng/dL in the TP AZ group. SHBG did not change significantly throughout in either group at all timepoints.

We demonstrated a reduction in the GTP suppression after TP insertion with the coadministration of AZ. We have no way of determining how much of the measured T was endogenous vs. exogenous, but our observed T levels in both groups after 120 days are comparable to those reported in series using AZ or TP as monotherapy. In our case series AZ was shown to be protective against GTP suppression in men on T supplementation and may have maintained or stimulated endogenous production of T. The addition of AZ to TP resulted in a prolongation of therapeutic T levels. This allowed for a longer period between reinsertions and may protect against testicular atrophy in long-term treatment. Some men (25%) regained sufficient endogenous T production

(>350 ng/dL) on AZ where reimplantation was not necessary over the period of observation. We demonstrated that in men who have undergone previous T replacement, the pituitary–gonadal axis can be stimulated with AZ to generate eugonadal T levels. It remains to be seen how long T levels can be sustained. Further studies are required to determine if an AZ "challenge" might be instituted prior to exogenous T therapy to assess the pituitary/gonadal reserve and function. Studies are also needed to prospectively assess the efficacy of AZ on relieving the symptoms of hypogonadism.

The major side effect of TP insertion was pain after insertion (7–14 days). In a retrospective safety analysis of 292 procedures using a similar technique to ours infection and extrusion were both reported at 0.3% [39]. We had no documented occurrences of extrusion or infection after insertion. One potential disadvantage of using long-acting TPs is the inability to rapidly reverse increases in T in certain situations such as a new diagnosis of prostate cancer. All men are screened with a prostate specific antigen (PSA) and digital rectal exams prior to TP insertion. No men developed prostate cancer during our period of observation.

Nonsteroidal AIs have been found to be well tolerated in men treated over a 1 to 2 years period [13,16,17,40,41]. Some studies have reported a transient mild increase in liver function tests in 5–7% of patients [16,17]. Liver function tests returned to baseline in these patients without their need to discontinue the medication. In the package insert no dose adjustment is required for patients with mild to moderate hepatic impairment. No changes in hematocrit or PSA have been reported with AZ [13,14,40]. In our series three patients discontinued AZ for vague gastrointestinal complaints (two diarrhea and one constipation). Hematocrit was routinely measured at 6 weeks and 4 months, and none of our patients had to discontinue treatment due to an elevated hematocrit. Although we did not specifically measure lipid profiles, a RPCT showed no increase in triglycerides with depo-T and AIs in combination after 3 months of treatment [19].

A common concern with the use of AI is their potential effect on bone health and metabolism. This has largely stemmed from the association of the use of AI in postmenopausal women who were found to have modest decreases in bone mineral density compared with placebo [41]. In men, there have been several studies investigating the effects of AI on markers for bone resorption and bone mineral density. Leder et al. did not find any significant effects of AZ on markers for bone formation or resorption after 3 months of AZ treatment [13].

The most widely referenced paper concerning the effects of AZ on bone metabolism is a 1-year double-blind RPCT in older men with hypogonadism [42]. The authors found no difference in bone markers but did report a decrease in the posterior–anterior spine bone mineral density from 1.12 g/cm^2 (±0.14) to 1.10 g/cm^2 (±0.14) after 1 year in the treatment group. The small decrease (0.02 gm/cm^2) achieved statistical significance only because the placebo group increased during the treatment period. Bone mineral density (BMD) in the femoral neck, total hip and total body BMD were not significantly different compared with placebo.

Interestingly, E2 levels in the Leder study remained in "the normal" range in the treatment group. Most studies utilizing AI report only a moderate decrease in estrogen levels [41]. In a study of the effect of AZ (2 mg/day) on bone metabolism, the authors suggested that the decrease in E2 is offset by increased local E2 production as a result of increased T levels [43]. Furthermore, E2 levels did not significantly change with T and AI combination therapy in a RPCT in epileptic men.

A weakness of this study is its retrospective nature and the nonuniformity of the laboratories and assays for the levels measured. Timing of blood draws was not standardized but in this age group, circadian variation in T levels is of doubtful significance [44]. Treatment satisfaction was not captured in the form of validated sexual function questionnaires. The sample size is small and longer follow-up is needed.

Despite the above weaknesses the findings are highly significant and suggest that the concomitant use of generic AZ with TP increases the interval between TP insertions and may thereby decrease long-term morbidity and cost. In addition 25% of men may not require subsequent implantation because of stimulated endogenous T production of AZ.

Conclusion

Men on TP AZ maintain therapeutic T levels longer than men on TP alone and have significantly less GTP suppression.

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Conflict of Interest: Andrew McCullough: Pfizer—data safety monitoring board, stock; Repros—consultant; Auxillium—consultant, speakers board, research grant; Antares—research grant; Endo—research grant.

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