



# Subcutaneous Testosterone Anastrozole Therapy in Men: Rationale, Dosing, and Levels on Therapy



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## Introduction

Testosterone (T) is the most abundant physiologic active hormone in both sexes, is essential for health and vitality throughout the lifespan of all mammals, and is the major source of estradiol in every organ system including the ovaries and testicles. Both adrenal and gonadal androgen production decline with age. This decline in bioavailable T at the cellular level contributes to mental and physical deterioration. Nonetheless, there are many misconceptions about the safety of T therapy. Most of these concerns, including cardiac and prostate safety, have been adequately refuted in recent years.<sup>1-6</sup>

The effect of T has been shown to be *dose dependent* in both men and women.<sup>2,7-10</sup> However, guidelines from specialty societies and labeling from the U.S. Food and Drug Administration (FDA) continue to recommend lower and often inadequate dosing for subcutaneous implants.<sup>11-13</sup> Despite the absence of data, some guidelines continue to recommend monitoring T levels on therapy and adjusting the dose based on a serum level. Measuring T levels and maintaining them in “mid range” has not been shown to provide optimal clinical results. Equally important, higher serum levels of T (without elevated estradiol) have not been shown to be a safety issue or associated with serious adverse events in either sex.<sup>7,14-17</sup>

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## Abstract

This analysis was designed to determine the efficacy of anastrozole, an aromatase inhibitor, combined with testosterone in a subcutaneous implant in preventing elevated estradiol levels and the subsequent side effects of excess estrogen associated with testosterone therapy. It also allowed for the establishment of normative ranges of serum testosterone levels on subcutaneous implant therapy. The study participants were 344 men who were accrued to an institutional review board-approved cohort study between April 2014 and 2017. Efficacy of the subcutaneous combination implant in maintaining low estradiol levels was evaluated. Serum levels of testosterone and estradiol were measured throughout the implant cycle, at week 4, and when symptoms returned. Correlations between patient demographics, dosing, and serum levels on therapy were evaluated. Mean testosterone dose was 1827 + 262 mg. Mean anastrozole dose was 15.3 + 3.2 mg with the majority of men receiving 16 mg of subcutaneous anastrozole. The mean interval of insertion was 4.8 months. Low estradiol levels were maintained throughout the implant cycle. Mean T level at week 4 was 1183 + 315 ng/dl and 553 + 239 ng/dl when symptoms returned. Levels of testosterone on therapy inversely correlated with body mass index. There were no adverse events attributed to testosterone or anastrozole therapy. Subcutaneous anastrozole delivered simultaneously with testosterone allowed for higher dosing of testosterone and less frequent intervals of insertion. Low-dose anastrozole released from the combination implant maintained low estradiol levels throughout the implant cycle and prevented clinical side effects attributed to excess estrogen.

The inadequacy of a single T level in adjusting dosing is not unexpected in light of significant inter-individual, intra-individual, and circadian variation of hormone levels in serum as well as assay variability. Hormone therapy remains both a science and an art, relying on the treating physician's judgment

and most importantly, the patient's response to therapy. As with all medications, dosing should be based on response to therapy and side effects of therapy.<sup>18</sup> Inadequate dosing and under-treatment of low T can adversely affect patient morbidity, mortality, and quality of life.<sup>2,19-21</sup>

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Many side effects attributed to T therapy are due to aromatization and excess estradiol at the cellular level (intracrine, autocrine, paracrine), which may or may not be measurable in serum. The extent of aromatization varies in different organ systems, varies between individuals, and is dose dependent with T.<sup>22-24</sup> Critical considerations when monitoring adverse effects in older, sicker populations include factors known to increase aromatase activity, such as<sup>25-27</sup>:

- insulin resistance,
- medication use,
- obesity,
- stress, and
- xeno-estrogens/toxins.

Side effects and symptoms of excess estrogen include<sup>14,15,27</sup>:

- aggression,
- anxiety,
- breast pain,
- erectile dysfunction,
- fluid retention,
- gynecomastia,
- increased thrombosis,
- irritability,
- lack of effect from T therapy, and
- weight gain.

Elevated estradiol levels are associated with peripheral artery disease, coronary thrombosis, and stroke.<sup>27-31</sup> In addition, excess estrogen, particularly in combination with low T, has an adverse effect on the prostate gland and may be causal in both benign prostatic hypertrophy and prostate cancer.<sup>26,27,32</sup> Also, elevated hemoglobin and hematocrit, a known dose-dependent effect of T, may be partially contributed to by higher estradiol levels.<sup>33</sup> Oral aromatase inhibitors have been used “off label” in men and have been shown to<sup>34-39</sup>:

- decrease seizure frequency,
- delay epiphyseal maturation,
- improve lipid and glucose metabolism,
- increase fertility,
- mediate the tropic effect of T on the prostate gland,
- raise T levels, and
- treat male breast cancer successfully.

Although subcutaneous T implants have been used in both sexes since 1937, and were FDA approved for men in 1972, there is a lack of published data on dosing and therapeutic ranges on therapy particularly when used in combination with an aromatase inhibitor. It would be expected that by preventing excess aromatization, higher, more clinically effective levels of T could be achieved without the safety concerns associated with elevated estrogen.

This analysis was designed to determine the efficacy of anastrozole, an aromatase inhibitor, combined with T in a subcutaneous implant in preventing elevated estradiol levels. It also allowed for the establishment of normative ranges (serum T levels) on T implant therapy, including ranges for when clinical symptoms returned.

## Materials and Methods

### TESTOSTERONE DOSING AND AROMATASE INHIBITOR THERAPY

Anastrozole, an aromatase inhibitor combined in the pellet implant, was initially used in 2009 to treat breast cancer patients and men with signs and symptoms of estrogen excess (TABLE 1). Early dose-finding studies in men confirmed that low-dose anastrozole (8 mg to 16 mg) released continuously over three months was able to prevent excess aromatization (Supplement 1). As the dose of T was increased over the years to increase clinical efficacy and duration of symptom control, it was shown that more men benefited from anastrozole therapy.<sup>39</sup>

### SUBCUTANEOUS PELLET IMPLANTS

Subcutaneous implants provide continuous release of active ingredients over a (dose-dependent) period of 2 to 5 months in men. The mixture of T and an aromatase inhibitor in a unitary implant provides simultaneous, continuous zero-order release and subsequent continuous delivery (24 h/day) of both active ingredients to the cellular level where aromatization takes place.

Subcutaneous T implants currently used in this clinical practice (RG) are composed of Testosterone Non-micronized Powder USP (Lot 99225A; Medisca, Plattsburgh, New York; and Lots 5100-150419/M, 15130-BB27-PR00002, 15K24-BB02-PR0034, 15L11-

**TABLE 1.**

### INDICATIONS FOR AROMATASE INHIBITOR THERAPY IN MEN.

(Elevated estradiol levels prior to or on testosterone therapy.)

Signs and symptoms of excess estrogen:

- Abdominal obesity, weight gain
- Anxiety, irritability, aggression
- Fluid retention, bloating
- Gynecomastia, breast pain
- Lack of effects from testosterone therapy

Medical indications:

- Benign prostatic hypertrophy
- History of prostate cancer
- Increased risk for thrombosis
- Insulin resistance
- Medications that increase aromatase activity
- Migraine headaches
- Obesity
- Seizures

13B02-PR00037; B&B Pharmaceuticals, Inc.; Englewood, Colorado) and Stearic Acid USP (Lots 100868/C, 107729/H, 126057/L; Medisca). Combination testosterone + anastrozole implants (T + A) are currently compounded with a geometric ratio (15:1:1) of T Non-micronized USP, Anastrozole (A) USP (Lots 104687/C, 101376/6, 104687/B, 108056/F, 122439/D, 124839/K; Medisca; and Lots 5054-2015-0205, 15124-BB03-PR00048; B&B Pharmaceuticals, Inc.) and stearic acid. T and T + A pellets are compressed with 2000 pounds of pressure using a standard pellet press into either 3.1-mm or 4.5-mm diameter cylinders, sealed in glass ampules/vials, and sterilized at 20 psi to 25 psi of pressure at 121°C (250°F) for 25 (T + A) minutes or 40 (T) minutes. Sterility testing for pellets was outsourced. For men, T implants (alone) are currently compounded as 4.5-mm, 200-mg implants. The T + A combination implants most often used (since 2014) in this practice are 4.5-mm implants containing 120 mg of T and 8 mg of anastrozole. Previously, the combination implants were compounded as a 3.1-mm diameter implant composed of 60 mg T and 4 mg of anastrozole, which are currently used in female patients and male patients who are treated with 3.1-mm,

75-mg T implants. Clinical effect and interval of insertion are dose dependent and not related to the diameter of the implant. Sterile implants are inserted into the subcutaneous tissue of the upper gluteal area or flank through a small incision using local anesthesia and a disposable trocar kit (Trocarkit.com).

## PATIENT SELECTION

An institutional review board-approved cohort study was initiated in March of 2014 to prospectively investigate the occurrence of cardiovascular events and prostate cancer in men treated with T therapy. All men currently treated or beginning treatment with subcutaneous T or T combined with anastrozole in the implant (T + A) were invited to participate in the study. No patient was excluded, including patients with a prior history of cardiac disease, prostate disease, or prostate cancer. All patients signed a written consent, which included information on the “off-label” use of anastrozole. A modified Aging Male Scale (AMS) questionnaire was used to document symptoms. A custom, web-based application using Microsoft Active Server Pages with a MySQL database backend system was developed to prospectively follow and track study patients. Date of the first T implant insertion, dose, and date of each subsequent insertion, along with patient identifiers, were entered. In addition, data and lab results were entered into an Excel sheet.

The study participants were 344 men who were accrued to an institutional review board-approved cohort study between April 2014 and 2017, at which time accrual was closed. Data were evaluated in April of 2017. Patient demographics are listed in **TABLE 2**.

## DATA COLLECTION AND ANALYSIS

To determine efficacy of the T + A implants in controlling serum estradiol on high dose (>1600 mg) T implant therapy, serum levels of T and estradiol were measured throughout the implant cycle in male patients receiving the combination therapy.

In order to determine therapeutic ranges on implant therapy, serum T and estradiol

levels were specifically evaluated at two time points: 1) 4 weeks after insertion and 2) at the end of therapy when patient’s symptoms returned prior to re-insertion (i.e., “end levels”). Hemoglobin and hematocrit were also monitored. Pearson product-moment correlations were performed to evaluate the extent and nature of the relationship between patient demographics (weight and body mass index [BMI]), dosing, baseline T levels, and serum levels (T, estradiol, hemoglobin, hematocrit) on T therapy. In addition, to further evaluate the relationship between BMI and measurable levels of T and estradiol on therapy, serum levels were separated by BMI: <25, 25-<30, 30-<35, and >35.

Due to the nature of real-life data, laboratory results were available from multiple labs and varying assays with carrying sensitivities. In order to calculate mean and SD values of estradiol levels and T levels reported as less than (<) or greater than (>), estimates were made based on an average of existing data in our patient population for that given range (Supplement 2).

## Results

### TESTOSTERONE DOSING

Similar to women, T implant dosing in men is weight based. Larger men require higher doses of T therapy. Also, duration of therapy is dose-related; higher doses of T maintain symptom control for longer periods of time. Prior to 2009, T dosing ranged between 800 and 1200 mg. However, symptoms returned in many men between

**TABLE 2.**

### PATIENT DEMOGRAPHICS.

CHARACTERISTIC	n=344
Age 1st insertion, y	52.92 + 9.85 (range 27.7 to 81.1)
Age evaluation, y	57.74 + 10.54 (range 27.7 to 84.7)
Height, inches (cm)	70.65 + 2.65 (179.45 + 6.72)
Weight, pounds (kg)	207.88 + 35.34 (94.49 + 16.06)
Body Mass Index	29.31 + 4.53
Testosterone baseline, ng/dl	300.63 + 110.16

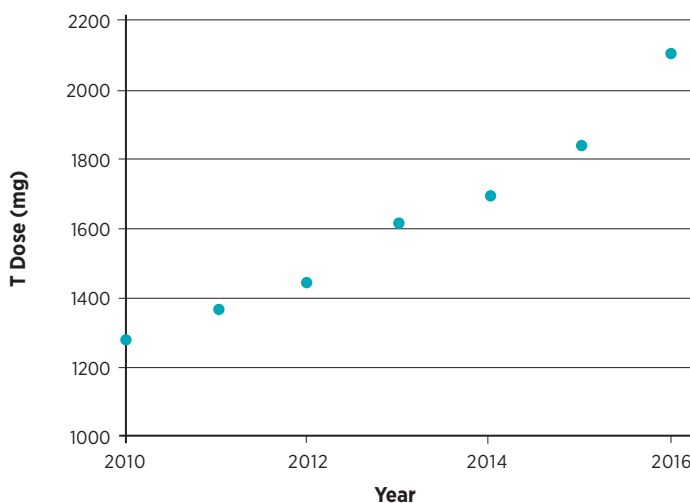
6 and 10 weeks. With increasing clinical experience, T dosing in male patients has gradually increased over the past 10 years and has remained stable since 2016 (**FIGURE 1**). Currently, on average, a 200-pound (90 kg) man is likely to receive approximately a 2000-mg T dose. Dosing is adjusted based on response to therapy (clinical efficacy) and side effects.

### AROMATASE INHIBITOR THERAPY

The use of anastrozole in combination with testosterone has also increased over the years due to the increased dosing of T and awareness of side effects of excess estrogen. In 2010, with an average T dose 1275 mg, 30 percent of men were treated with anastrozole. This increased to 67

**FIGURE 1.**

### MEAN TESTOSTERONE IMPLANT DOSE IN MALE PATIENTS TREATED BETWEEN 2010 THROUGH 2016.



percent in 2011 (mean T dose of 1369 mg) and 88 percent by 2012 (mean T dose of 1444 mg). The majority of men treated with a T dose of 1600 mg or greater benefited from subcutaneous anastrozole.

### EFFICACY OF SUBCUTANEOUS ANASTROZOLE THERAPY

The efficacy of anastrozole in maintaining serum estradiol levels below 30 pg/mL has been demonstrated in the past (Supplement 1). This has been further verified by recent data at higher dosing regimens.<sup>39</sup> **FIGURE 2** represents 541 data points over 6 months (cycle duration) of T + A therapy and illustrates zero-order release of T reflected by the decline of serum T levels over the clinical lifespan of the implants. Testosterone is measured in ng/dl, 10-fold higher units than estradiol. **FIGURE 3** shows the maintenance of low estradiol levels in patients over the entire time period or lifespan of the pellet implants supporting the continuous delivery and zero-order release of both active ingredients from the T + A implant, which is identical to the delivery and release rate of T from T implants. There is a minimal trend towards increasing estradiol levels over time (Days 2 through 182) as the anastrozole wears off.

### RANGES ON THERAPY

Testosterone levels are dose dependent. Levels peak at 24 to 48 hours following implantation and gradually decline thereafter. The mean T dose in study patients April 2014 through April 2017 was 1827 + 262 mg. Of the 344 patients, 339 (98.5%) were treated with an aromatase inhibitor combined with T in the unitary implant (T + A). The mean subcutaneous anastrozole dose was 15.3 + 3.2 mg with the majority of men receiving 16 mg of anastrozole. The mean interval of insertion for patients receiving implants in the last quarter of

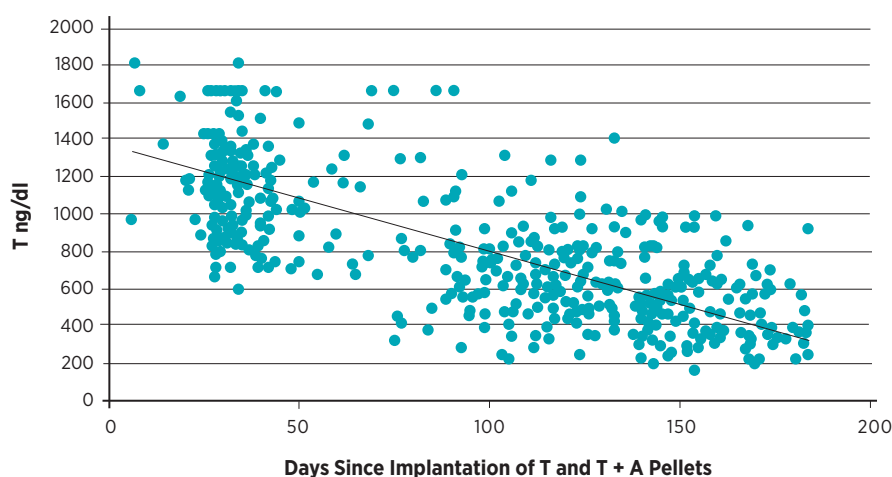
2016 ( $n=148$ ) was 4.8 months (144.2 + 33.3 days). Levels on therapy are presented in **TABLE 3**.

### CORRELATIONS ( $n=344$ )

Correlations between patient demographics (weight and BMI), dosing of T and anastrozole, baseline T levels, and serum levels at week 4 and at the “end” (i.e., levels on therapy when patients became symptomatic prior to re-insertion) are presented in **FIGURE 4**. As expected, T dose positively correlated with body weight and BMI. Also, obese men often require higher doses of anastrozole, as fat is a major source of aromatase activity. It should be noted that hemoglobin and hematocrit positively correlated with “end” levels of both T and estradiol. However, week 4 estradiol levels more strongly correlated with hematocrit compared to week 4 T levels. Interestingly, BMI inversely correlated with measured T levels on therapy. T levels remained significantly higher throughout the cycle in patients with lower BMI compared to patients with a higher BMI despite lower dosing (Supplement 3). T levels declined at a rate of 0.7% to 0.8% per day in all groups (BMI <25, BMI 25-<30, BMI 30-<35, BMI >35). Estradiol levels increased at a rate of approximately 0.25% per day, notably at a slighter greater rate in men with higher BMI >35 ( $P=0.09$ ), but remained low (therapeutic) in all groups. Intercepts, which reflected levels at the beginning of therapy, varied for T but not for estradiol. The T intercept for BMI <25 is 1604 ng/dl compared to approximately 1200 ng/dl in men with a BMI >35 (Supplement 3). Also, thinner men with lower BMI, had higher measurable T levels at week 4 and when symptoms returned (end levels) despite significantly lower dosing. The mean T level when symptoms returned in men with a BMI <25 was 650.5 ng/dl compared to 586.4 (BMI 25-<30), 567.9 ng/dl (BMI 30-<35), and 514.7 ng/dl (BMI >35).

**FIGURE 2.**

#### TESTOSTERONE LEVELS OVER TIME.



### ADVERSE EVENTS

Mean length of therapy at the time of analysis was 4.8 + 3.1 years (range 0.17 to 11.6 y). No patient on T + A therapy had been diagnosed with prostate cancer. As previously reported, there has not been an increase in venous thrombotic events.<sup>14</sup> One patient died of untreated (suspected) cardiac disease. There have been no deaths or adverse drug events other than elevated hemoglobin and hematocrit attributed to T therapy. There have been no side effects or adverse reactions to low-dose subcutaneous anastrozole including body aches, joint pain, and gastrointestinal side effects, which are common with oral delivery.

### Discussion

T effect is dose dependent.<sup>2,7-10</sup> However, T is aromatized to estradiol, resulting in a dose-



dependent increase in estradiol. Despite adverse effects caused by excess estrogen, monitoring serum estradiol levels is not a recommendation in current guidelines on T therapy<sup>11</sup> and is rarely performed in clinical practice. Even journal articles that report on adverse events associated with T therapy often fail to report estrogen levels on therapy,<sup>40,41</sup> which may be a contributing factor for cardiovascular side effects including edema, fluid retention and subsequent worsening of heart failure, and thrombosis.<sup>42</sup>

The combination of T with an aromatase inhibitor has allowed for higher dosing of T at longer intervals of insertion without the associated side effects due to excess estrogen. Currently, the average interval of insertion is 4.8 months (144 days). Prior to the “high-dose” regimen, patients would complain of symptoms returning within 6 to 12 weeks of insertion, which is consistent with the literature.<sup>13</sup>

We have shown that low-dose anastrozole combined in the pellet implants provides sustained therapeutic levels of T without elevation of serum estradiol and more importantly, no adverse symptoms related to excess estrogen, including<sup>14</sup>:

- Anxiety
- Gynecomastia
- Breast pain
- Increased thrombosis
- Edema
- Irritability
- Fluid retention
- Prostate issues

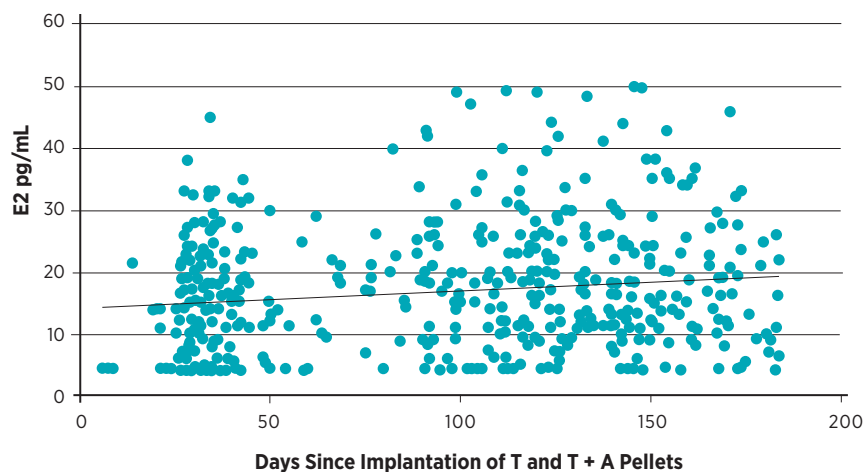
The sustained-release combination implants containing a total of 16 mg of anastrozole releases approximately 0.1 mg of anastrozole per day compared to an oral dose of 1 mg per day used in breast cancer patients. This low dose is able to prevent excess aromatization in the majority of male patients treated with approximately 13 mg per day of T released from the T and T + A implants.

T and anastrozole are released simultaneously from the compounded combination implant. With a ratio of 15:1 (or 10:1), T drives the release of anastrozole at a rate identical to T alone, as shown by our *in vivo* data/clinical results and prior *in vitro* dissolution analyses. *In vitro*, an implant of letrozole alone, did not dissolve in a fat-soluble medium (Supplement 4) and would not release simultaneously (if at all) with fat-soluble T *in vivo*. In addition, there is no data demonstrating that hydrophilic aromatase inhibitors release or are clinically effective when delivered as a subcutaneous implant (alone) in fatty, subcutaneous tissue.

A theoretical concern is that autoclaving does not sterilize the implants. However, implants have been sterilized via autoclave for over 70 years without concern. We use the same autoclave settings for T

**FIGURE 3.**

**ESTRADIOL LEVELS ON TESTOSTERONE AND ANASTROZOLE THERAPY OVER TIME.**



implants as the FDA approved (75-mg T pellet). No batch of pellets has failed sterility testing. Although there are other options for sterilizing implants, autoclaving has a secondary function of heat-fusing the pores of the implant and thus slowing release. We have found this to be true in dissolution studies where implants that are not autoclaved do dissolve at a faster rate over time (Supplement 4). This should remain a concern until proven otherwise in pre-clinical or clinical studies.

Not surprisingly, there have been no side effects from subcutaneous anastrozole therapy including bone pain, joint pain, or hot flashes. As expected, obese patients and patients treated with higher doses of T require higher doses of anastrozole. In clinical practice, the dose of anastrozole is increased based on estradiol levels (usually >30 pg/mL to 40 pg/mL), and, more importantly, symptoms of estrogen excess including lack of effect from T.

**TABLE 3.**

**LEVELS ON THERAPY.**

LEVELS ON THERAPY	MEAN + SD %
T (ng/dl) week 4	1183 + 315
>1500	25%
>1100	65%
E2 (pg/mL) week 4	14.3 + 10.6
< 5	15%
<15	54%
> 30	9%
> 50	1%
T (ng/dl) “end”*	553 + 239
E2 (pg/mL) “end”*	18.7 + 12.3
< 5	10%
<15	44%
> 30	14%
> 50	1.5%
Hemoglobin (g/dl)	16.14 + 1.37
Hematocrit	48.03 + 4.15

\*“End” refers to levels on therapy when patients became symptomatic prior to re-insertion.

**FIGURE 4.****PEARSON PRODUCT-MOMENT CORRELATIONS.**

	Weight	BMI	t. dose	a. dose	t.4wk	e2.4wk	t.end	e2.end	hb	hct	t.base
Weight	1	0.88	0.55	0.5	-0.19	-0.02	-0.17	0.23	0.2	0.23	-0.24
BMI	0.88	1	0.49	0.49	-0.24	0.05	-0.23	0.26	0.16	0.2	-0.24
t. dose	0.55	0.49	1	0.36	-0.01	0.06	0.04	0.23	0.11	0.16	-0.12
a. dose	0.5	0.49	0.36	1	-0.19	-0.12	-0.05	0.16	0.09	0.14	-0.15
t.4wk	-0.19	-0.24	-0.01	-0.19	1	0.31	0.38	0.15	0.05	0.06	0.24
e2.4wk	-0.02	0.05	0.06	-0.12	0.31	1	0.2	0.39	0.11	0.17	-0.04
t.end	-0.17	-0.23	0.04	-0.05	0.38	0.2	1	0.27	0.29	0.36	0.08
e2.end	0.23	0.26	0.23	0.16	0.15	0.39	0.27	1	0.24	0.28	-0.18
hb	-0.2	0.16	0.11	0.09	0.05	0.11	0.29	0.24	1	0.95	-0.12
hct	0.23	0.2	0.16	0.14	0.06	0.17	0.36	0.28	0.95	1	-0.14
t.base	-0.24	-0.24	-0.12	-0.15	0.24	-0.04	0.08	-0.18	-0.12	-0.14	1

a = anastrozole; end = when symptoms returned; e2 = estradiol; t = testosterone

Therapeutic ranges on combination therapy have been established and shown to be safe in up to 12 years of therapy. The mean serum T level at week 4 was 1183 + 315 ng/dl with over 25% of men having a T level greater than 1500 ng/dl. There have been no side effects or complications from therapy at these levels. Estradiol levels remain controlled throughout the cycle of the pellet implant. Although 70% of men have a serum estradiol less than 15 pg/mL at month one, there have been no complaints of hot flashes due to estrogen deficiency. This can be explained by aromatase activity taking place at the cellular level, which is immeasurable in serum. Only when excess aromatization takes place (particularly with abdominal obesity) and estradiol spills over into the systemic circulation would estradiol be measurable in serum. An estradiol level of <5 pg/mL on subcutaneous T therapy is not concerning. Although bone loss is a consideration on oral aromatase inhibitor therapy (alone), this has not been observed in clinical practice with the lower dosing of anastrozole delivered in combination with higher doses of T, aromatase's major substrate.

T dosing should be based on the patient's response to therapy and side effects of therapy rather than a single T level. As mentioned in the introduction, a single T level is extremely variable, fluctuating greatly within minutes and throughout the day. Many factors affect the release of T from the implant and the "transient" level measured in serum, including: BMI, body temperature, heart rate, hormone assay/methodology, and hydration status.

Consistent with previous studies, lower BMI was associated with higher measured serum T levels on therapy despite lower "weight-based" dosing.

This does not infer that dosing should be lowered, as men with lower BMI become symptomatic at higher levels.

A strength of this study is that "end levels" were documented. Patients had T and estradiol levels measured when their clinical symptoms returned. Although some guidelines recommend that T levels should remain in mid range, this would not provide optimal therapy with subcutaneous T therapy. Many patients on T implant therapy become symptomatic despite T levels at or above mid range (e.g., 553 + 239 ng/dl on average; 650.4 + 255 ng/dl in men with a low BMI).

The minimum effective dose of T pellets in men is around 750 mg to 900 mg, which has not been shown to be optimal for control of symptoms.<sup>43</sup> Also, lower dosing requires more frequent intervals of insertion, increasing patient expense, inconvenience, and discomfort.

The maximum safe dose of T with aromatase inhibition has not been determined. In this clinical practice, men with a severe neurological disease like Alzheimer's and Parkinson's disease have required even higher doses of T (2600 mg) at more frequent intervals (8 weeks to 10 weeks) to preserve memory and function. There have been no serious side effects even at these higher doses.

## Conclusion

The continuous release of T and anastrozole from the combination implant prevents excess aromatization and enables higher T dosing at less frequent intervals of insertion while avoiding side effects from excess estrogen. Dosing should be adjusted based on clinical response to therapy and side effects from therapy, not a single serum T level. Estradiol levels should be measured, and patients should be monitored for signs and symptoms of excess estrogen.

## Contributors

Rebecca Glaser designed the study, participated in patient care, and collected all data. Anne York performed the statistical analyses. Both authors participated in data evaluation, the writing of the manuscript, and approved the final manuscript.

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