



AT THE FOREFRONT
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Medicine

Treatment of Vasomotor Symptoms in a Transgender Male After Hysterectomy

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Endocrinology Fellow

Disclosure Information

I have the following financial relationships to disclose:

- Consultant for: _____
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I will not discuss off label use or investigational use in my presentation.

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I will discuss the following off label use and/or investigational use in my presentation:

Estradiol

Patient HPI

- 35yo female to male transgender Pt presenting for continuation of testosterone
- Born genetically female but identifying as male since an early age
- Has been on testosterone for the past 4 years (Howard Brown Health)
- Since removal of ovaries & uterus has been having significant “hot flashes” reports occurring “every hour”
- Reports symptoms are “very bothersome and embarrassing” significantly disrupting daily life

Patient History

- PMH:
 - Gender dysphoria/Gender Incongruence
- PSH:
 - Salpingo-oophorectomy and hysterectomy in 7/2015
 - Double mastectomy in 2016 with chest revision 2/2017
- FH:
 - MGM gestational DM
- SH: Lives with his wife and son; He works as a plumber. Does not drink EtOH or smoke. No IVDU.
- Medications: Testosterone 100mg Q 2 weeks (recently reduced from 150mg Q2 weeks)

Physical Exam

- Vitals: BP 119/79, Pulse 87, Ht 5'4" Wt 65.7 kg BMI 24.8
- **African American patient, male presentation; in no apparent distress. Appears stated age.**
- HEENT: No pharyngeal edema. EOMI. **Facial hair present**
- Neck: No thyromegaly
- CV: RRR, no murmurs or peripheral edema
- Pulm/Chest: CTAB
- Abd: Soft, non tender, non distended; **male pattern hair on abdomen**
- Neuro: Alert & oriented, no focal deficits
- Skin: No bald spots, **no acanthosis nigricans**
- Psych: **Normal mood, thought content appropriate**



Treatment of Hot Flashes in Transgender Patients on Testosterone?



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Treatment of Hot Flashes in Transgender Patients on Testosterone?

Can we apply what we know about postmenopausal treatment in cis/natal women to transgender FTM patients?



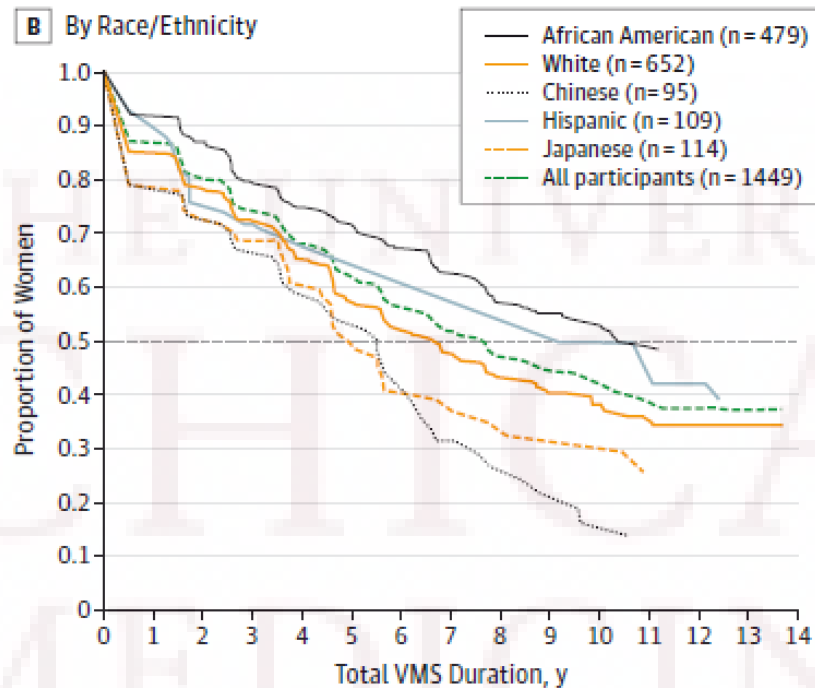
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Hot Flashes



- Hot flashes (vasomotor symptoms) occur in 75-80% of menopausal women in the US (natural or surgical menopause)
- Rapid & exaggerated heat dissipation response, consisting of profuse sweating, peripheral vasodilation, & feelings of intense internal heat
- Premenopausal women initiate mechanisms to dissipate heat when the core body temp increases by 0.4 C; this happens with much lower increases in temperature in menopausal women
- Due in part to estrogen depletion & elevated brain norepinephrine which narrows the thermo-neutral zone in the hypothalamus

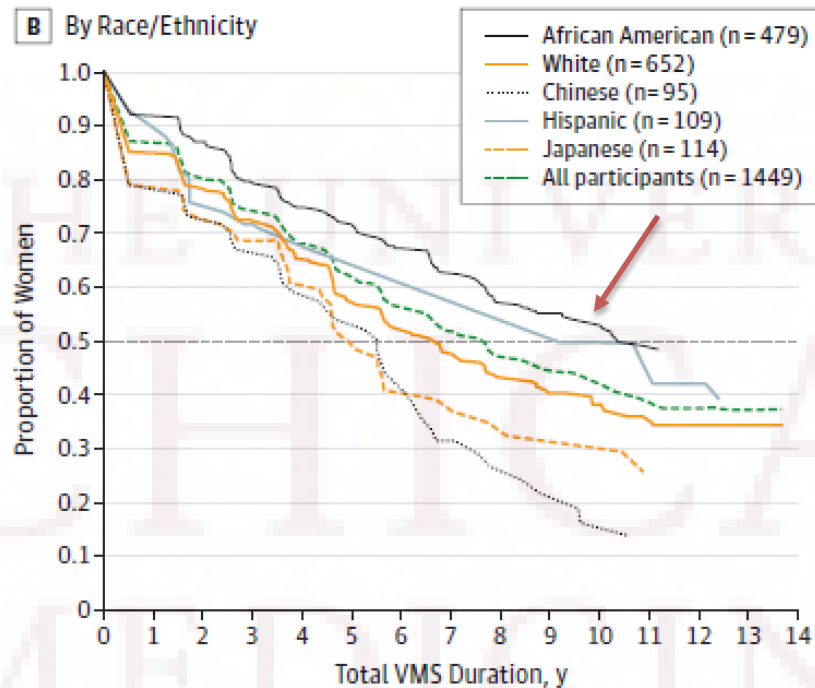
Kaplan-Meier Estimates of Total VMS Duration of Frequent VMS by Race/Ethnicity



JAMA Internal Medicine April 2015 Volume 175, Number 4

- Strongest estimates to date of total VMS duration over menopause in a multiethnic sample
- Analysis included 1449 women with frequent VMS (≥ 6 d in the previous 2 wks)

Kaplan-Meier Estimates of Total VMS Duration of Frequent VMS by Race/Ethnicity



- Frequent VMS lasted more than 7 years during the menopausal transition for >50% of women
- African Americans reported the longest total VMS duration (median 10.1 yrs)

Treatments for Hot Flashes

- **Nonpharmacologic:**
 - Behavioral measures: avoiding triggers (spicy foods, stress), relaxation based procedures, CBT
 - Weight loss, vitamin E, hypnosis, soy, black cohosh
- **Nonhormonal:** SSRIs (paroxetine), SNRIs (venlafaxine), anti epileptics, & centrally acting drugs (clonidine, gabapentin)
- **Hormonal therapy:** The most effective treatment for HFs
 - Estrogens alleviate HFs & prevent bone loss associated with menopause.
 - Estrogen & progestin (or SERM) for women with an intact uterus
 - Estrogen only for post-hysterectomy

Back to Our Patient: Goals of Testosterone Therapy in FTM Individuals

- To suppress endogenous sex hormone secretion
- To maintain testosterone levels in the physiologic normal male range (400-700 ng/dl)
- Avoid adverse events resulting from excess testosterone therapy
 - Erythrocytosis, sleep apnea, HTN, excessive weight gain, salt retention, lipid changes, & excessive or cystic acne

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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***Cosponsoring Associations:** American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Table 11. Hormone Regimens in Transgender Persons

Transgender females ^a	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate ^b	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate ^c	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6% ^d	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

^aEstrogens used with or without antiandrogens or GnRH agonist.

^bNot available in the United States.

^cOne thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

^dAvoid cutaneous transfer to other individuals.

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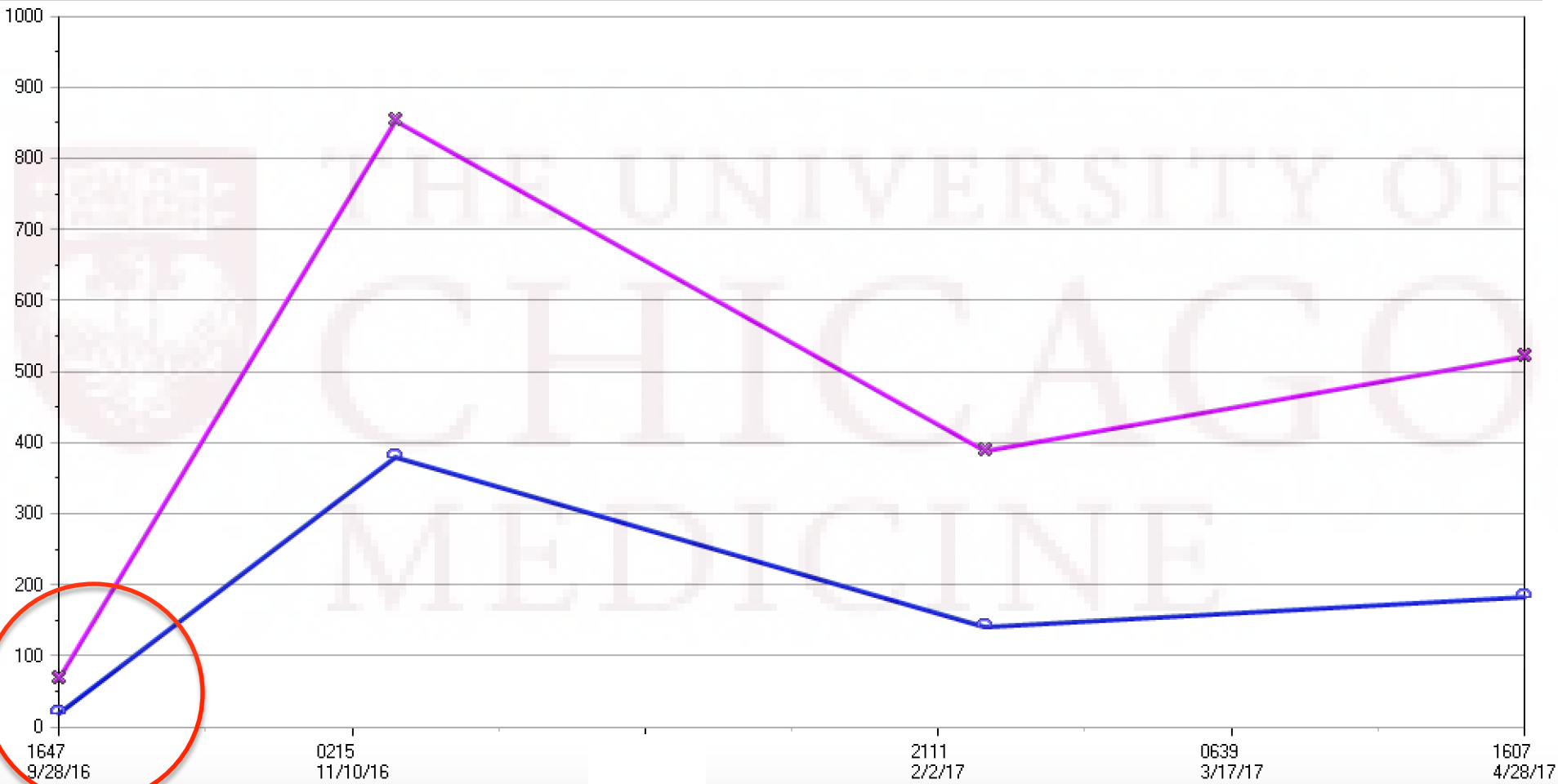
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Labs Upon Initial Visit With Other Provider

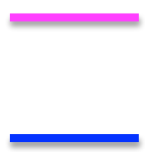
Graph (9/28/16 1647 - 4/28/17 1607)



Had run out of testosterone, reported HF symptoms did not get better or worse

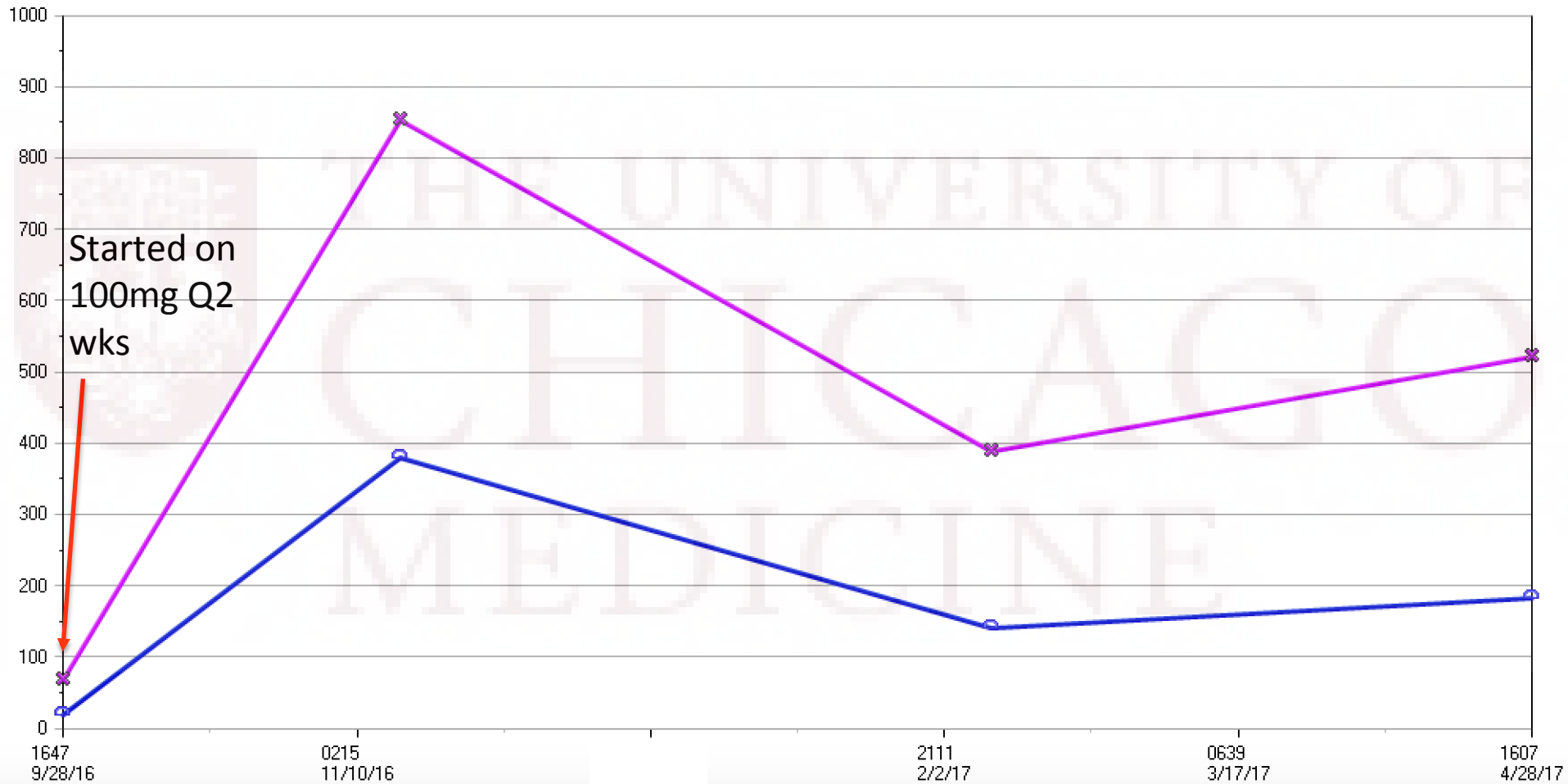
Total Testosterone

Free Testosterone



Testosterone Re-Started at Prior Dose

Graph (9/28/16 1647 - 4/28/17 1607)

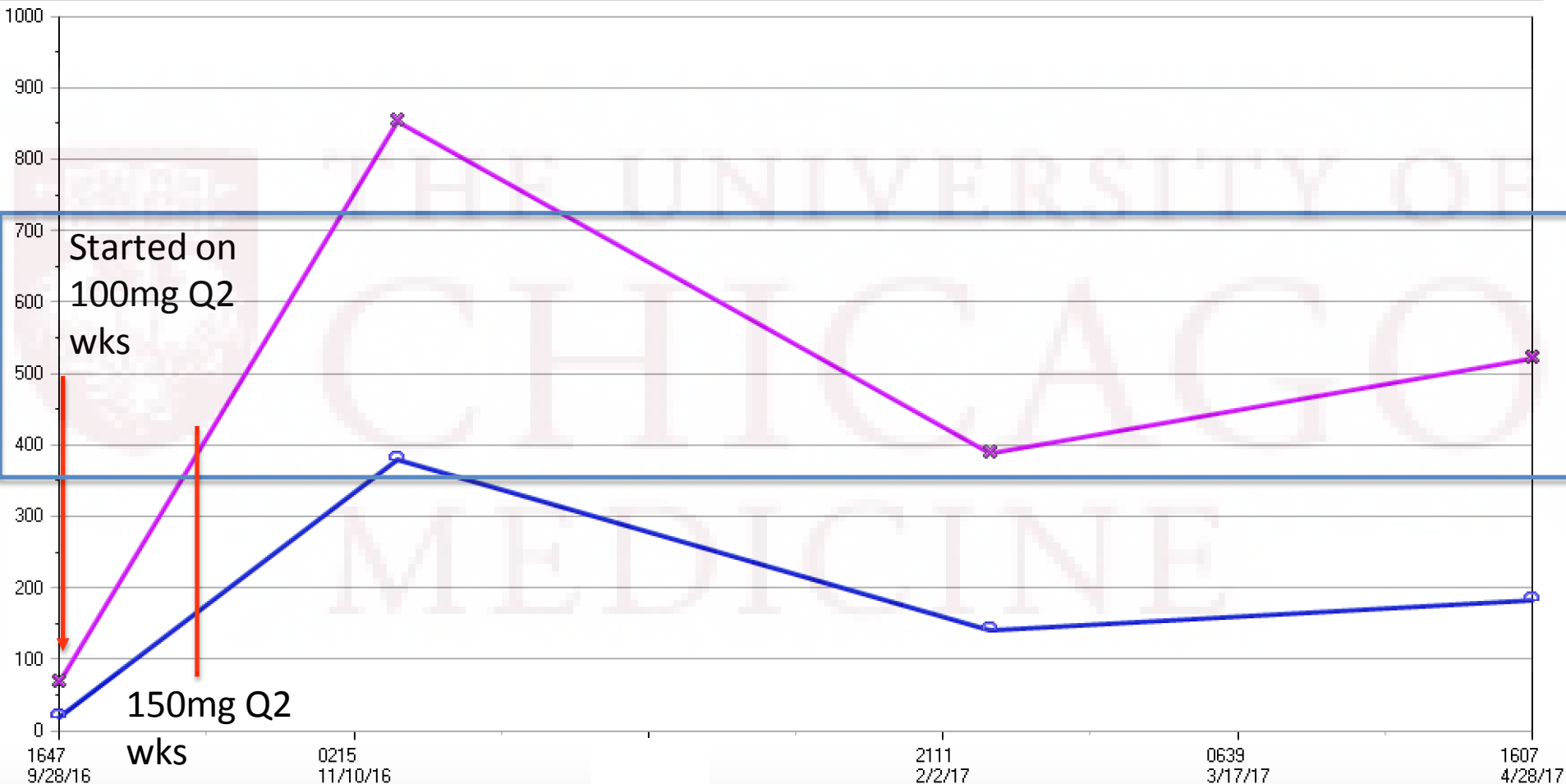


Total Testosterone

Free Testosterone

Testosterone Dose Increased Due to Continued Symptoms of HFs

Graph (9/28/16 1647 - 4/28/17 1607)



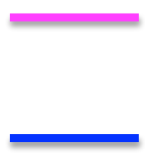
Started on
100mg Q2
wks

150mg Q2
wks

Told to return in 6 weeks for
repeat labs on 11/10/16

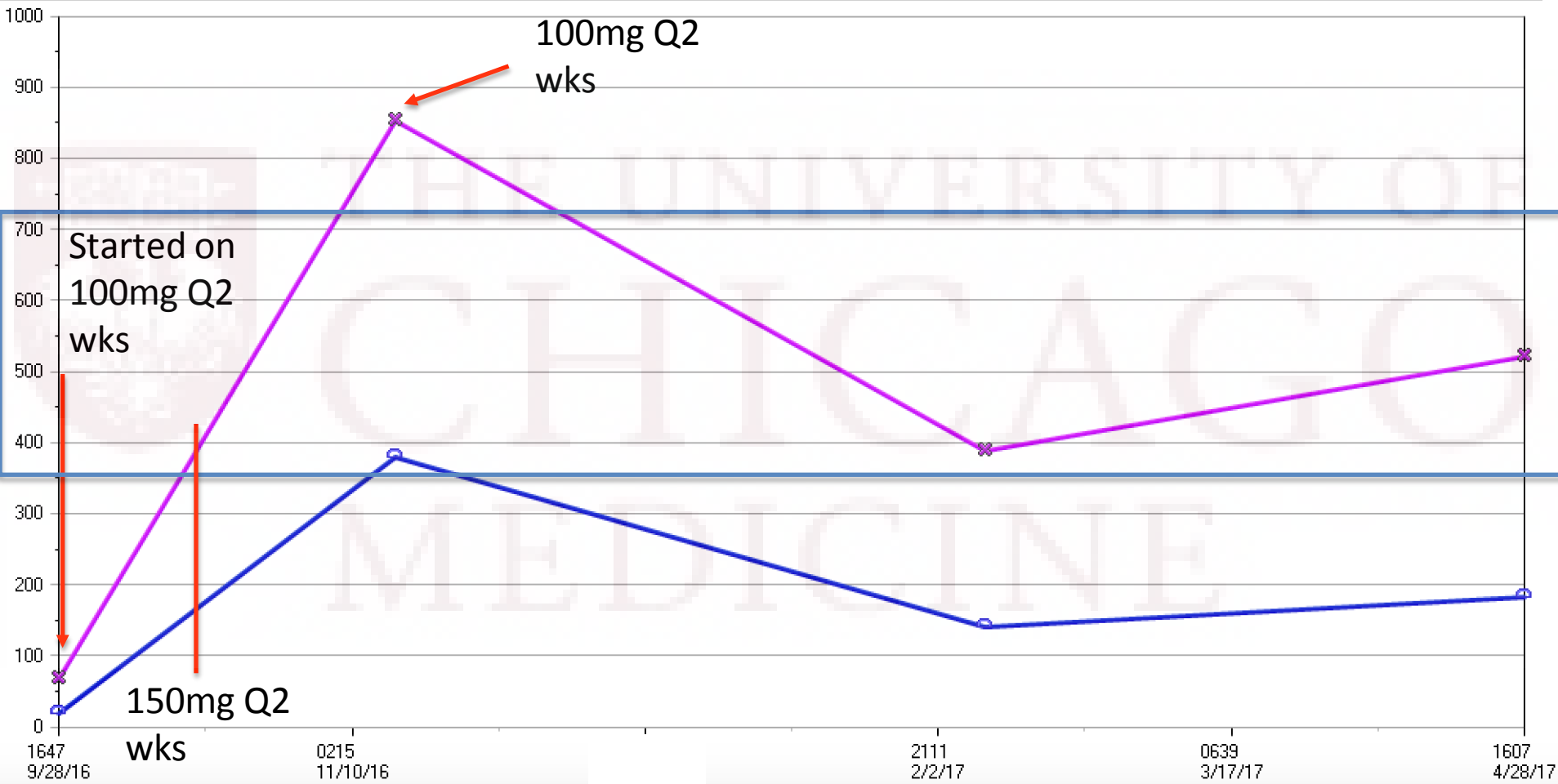
Total Testosterone

Free Testosterone



Testosterone Dose Reduced Due to High Testosterone Level

Graph (9/28/16 1647 - 4/28/17 1607)

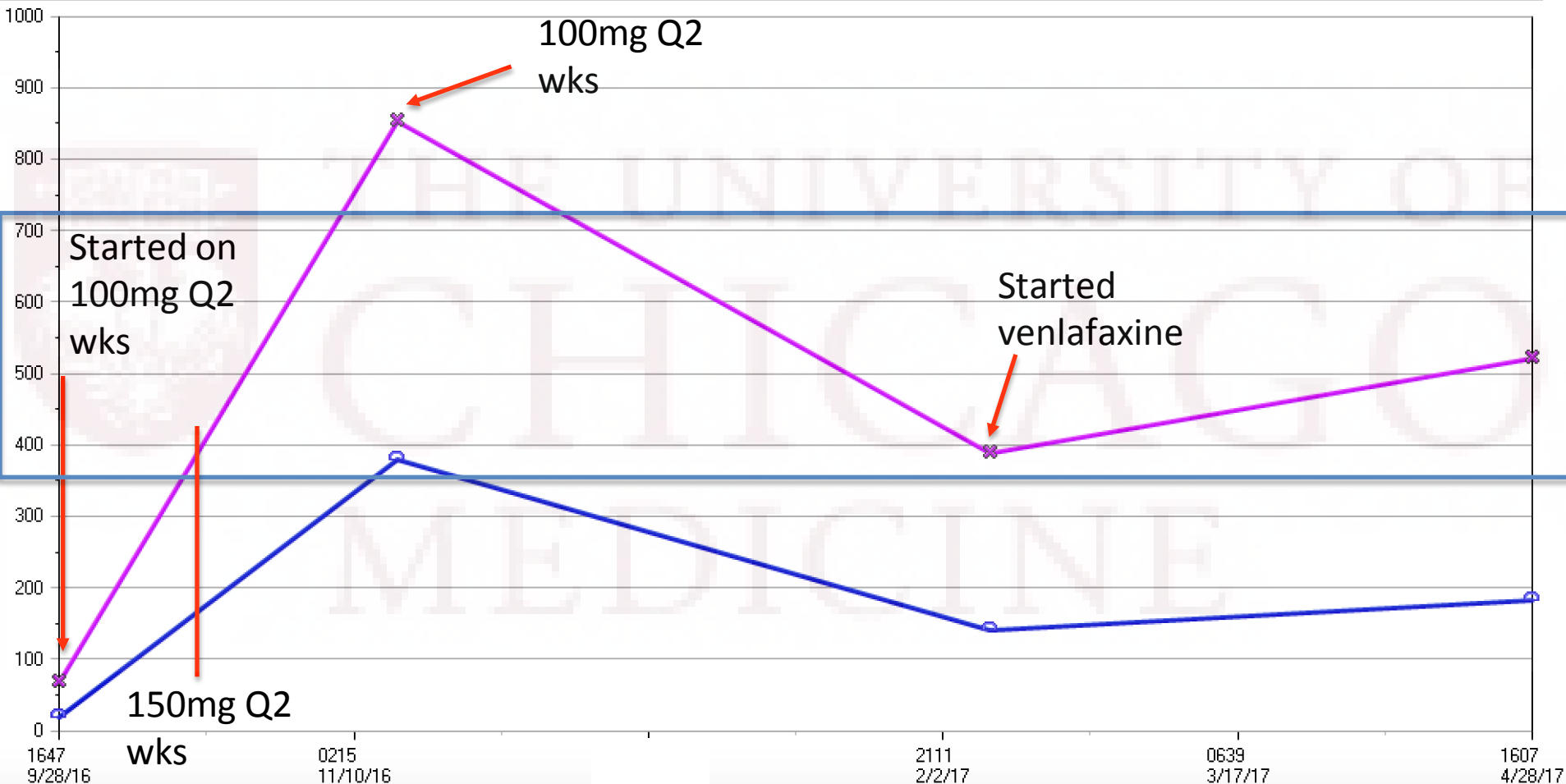


Total Testosterone

Free Testosterone

Started on SNRI for Symptoms of HFs

Graph (9/28/16 1647 - 4/28/17 1607)



Did not tolerate venlafaxine;
Only took for a few days

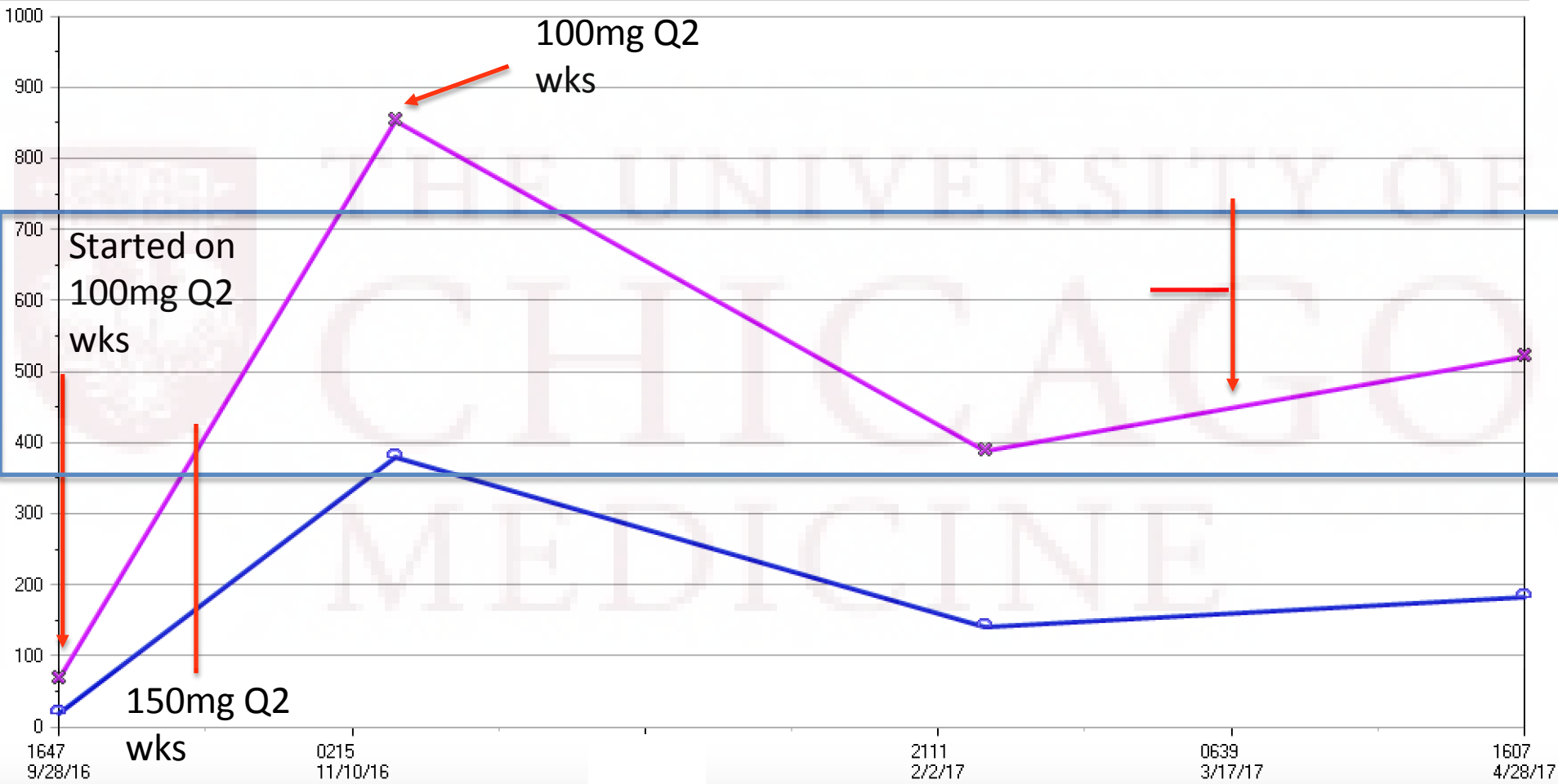
Total Testosterone

Free Testosterone



Venlafaxine Stopped; Discussed Efficacy of Treatments for Hot Flashes in Postmenopausal Women

Graph (9/28/16 1647 - 4/28/17 1607)

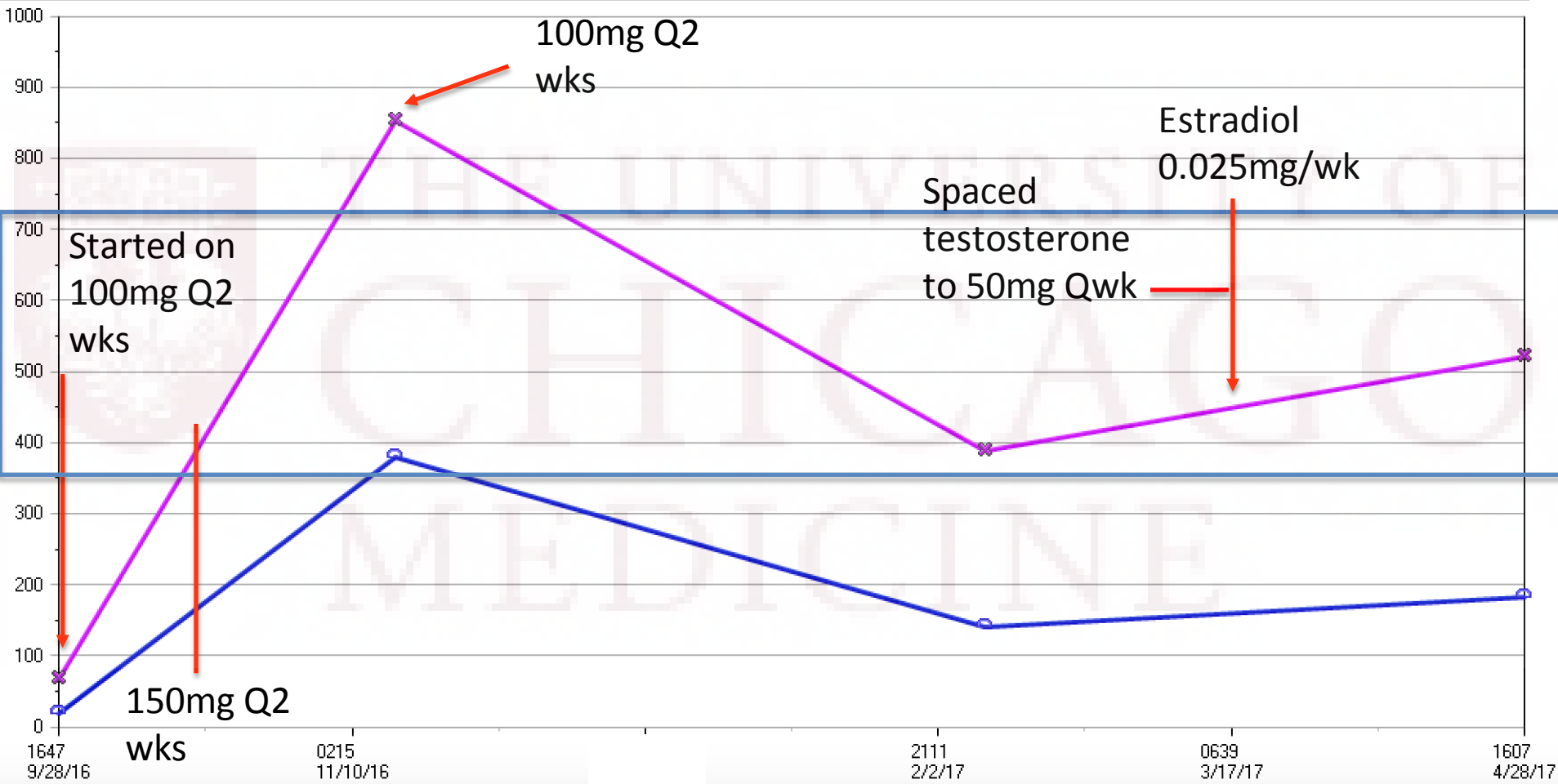


Total Testosterone

Free Testosterone

Testosterone Dosed Weekly & Low Dose Estradiol Started

Graph (9/28/16 1647 - 4/28/17 1607)

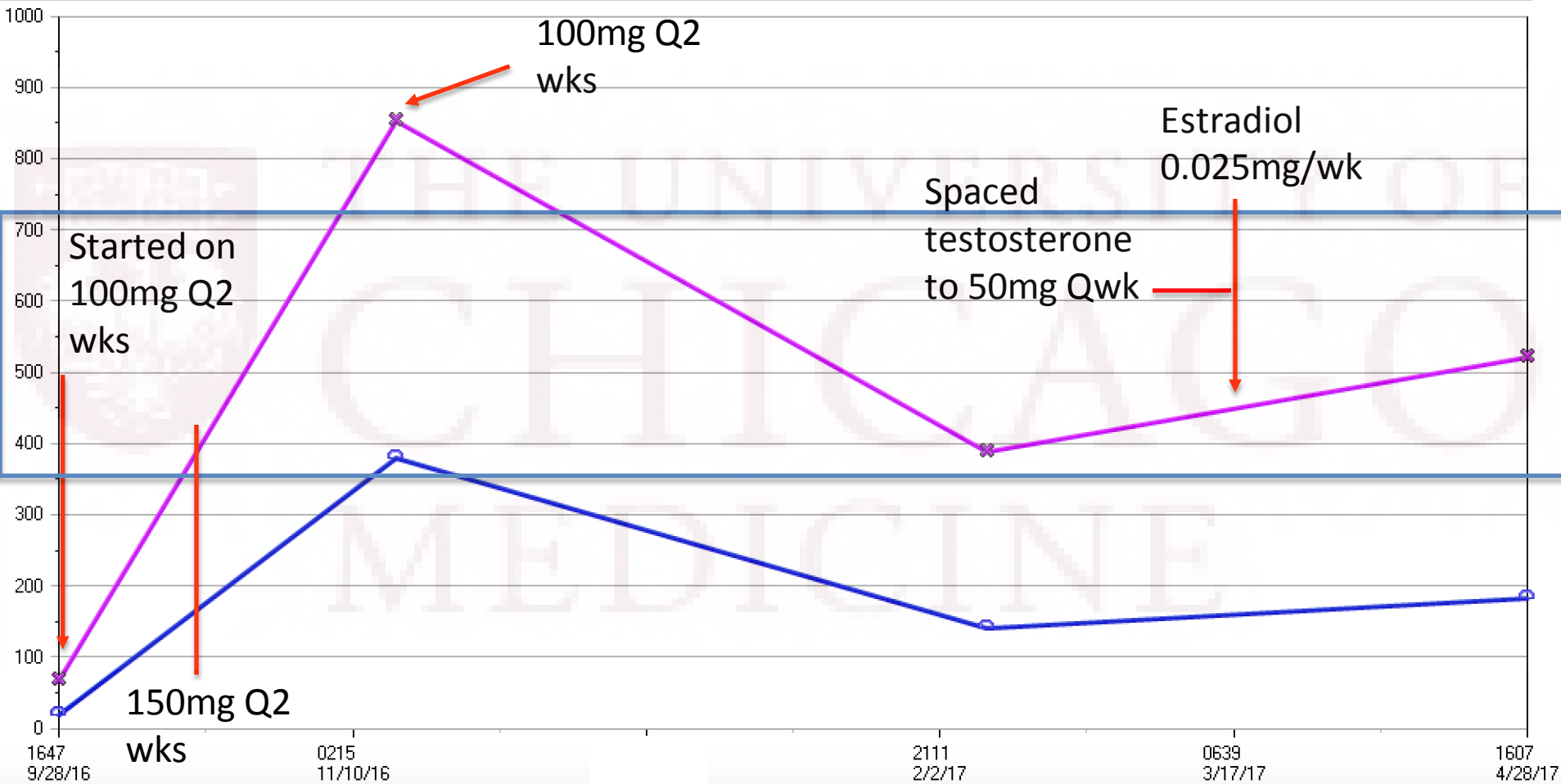


Total Testosterone 

Free Testosterone 

Testosterone Dosed Weekly & Low Dose Estradiol Started

Graph (9/28/16 1647 - 4/28/17 1607)



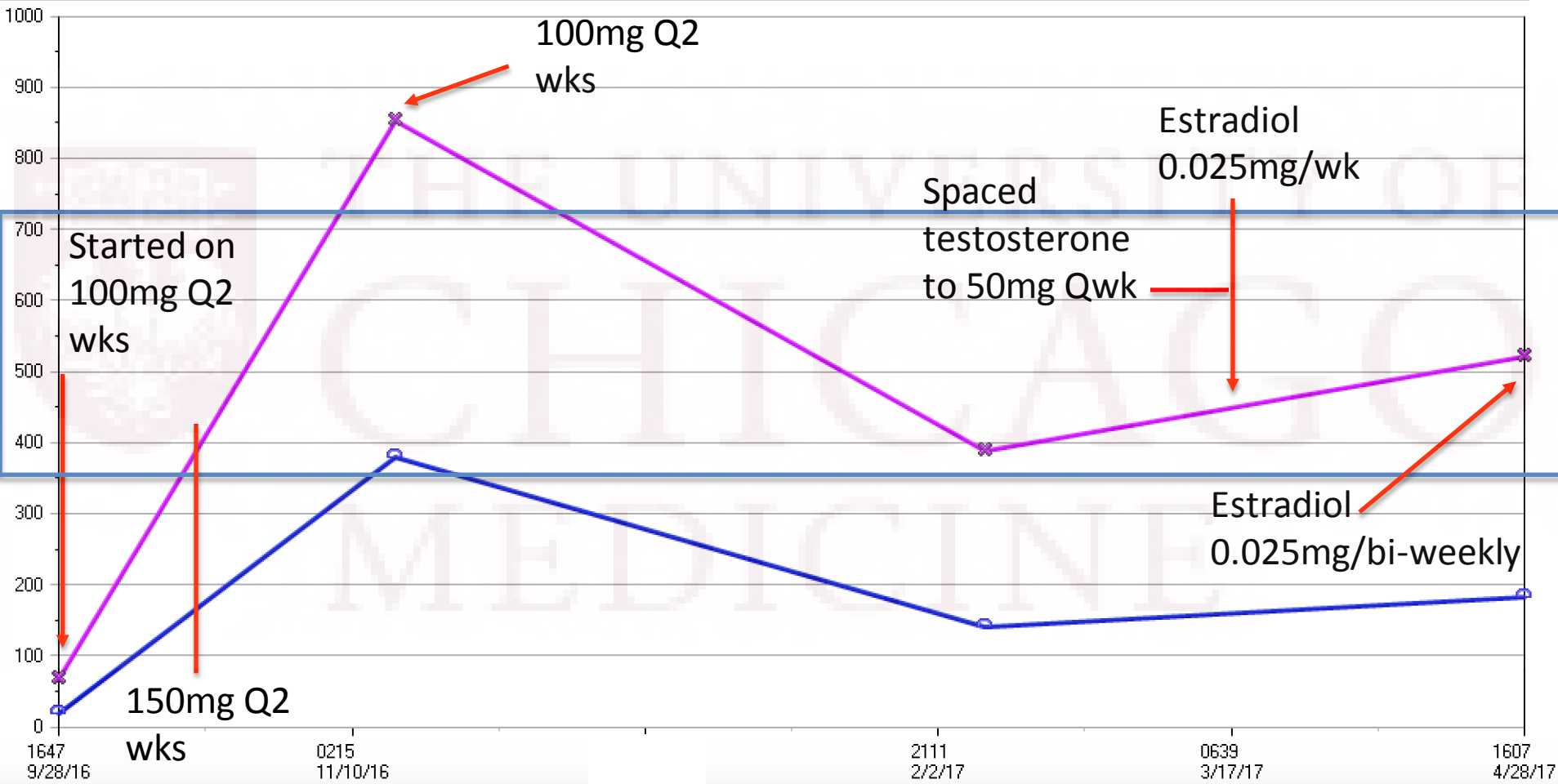
Symptoms of HFs improved, but improvement lasted ~3 days

Total Testosterone 

Free Testosterone 

Estradiol Patch Increased from 1 to 2x Week; Asked to Increase Testosterone to 80mg Qwk

Graph (9/28/16 1647 - 4/28/17 1607)

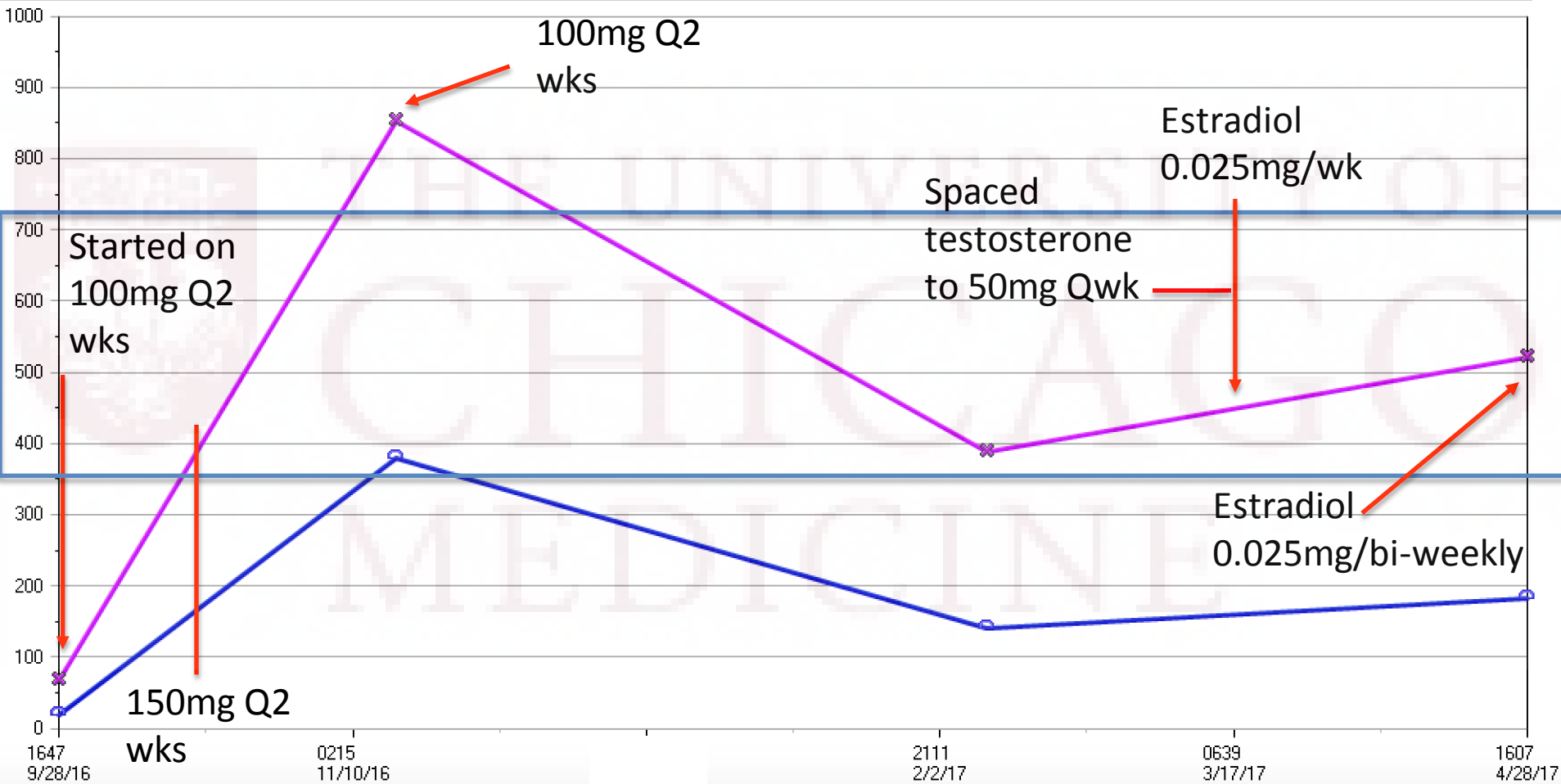


Total Testosterone



Free Testosterone

Estradiol Patch Increased from 1 to 2x Week; Asked to Increase Testosterone Dose

Graph (9/28/16 1647 - 4/28/17 1607)

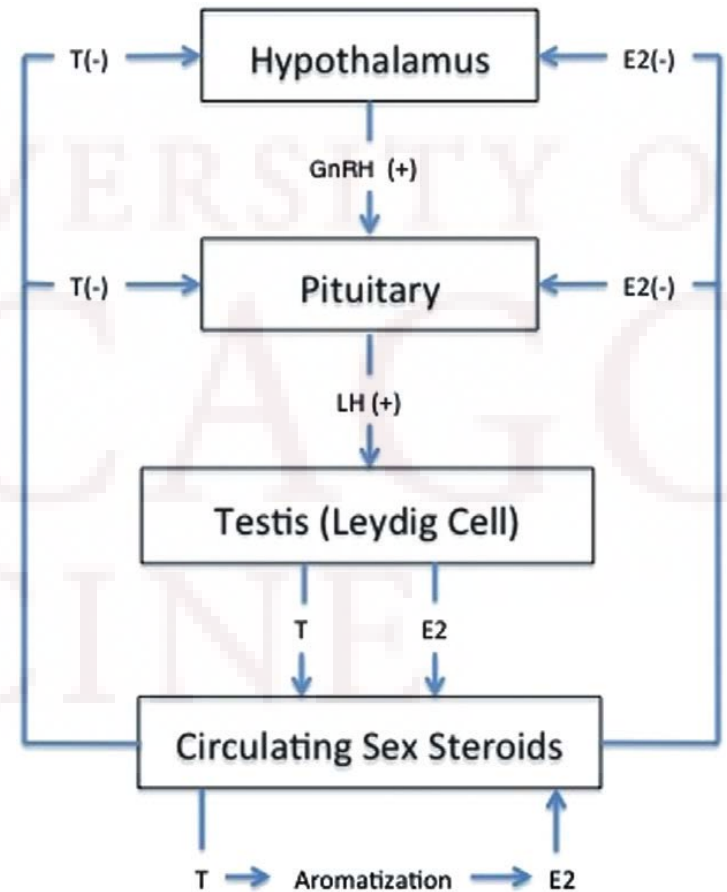


Pt continued T at 50mg Qwk;
Symptoms of HFs have resolved
with bi-weekly estrogen patches

Total Testosterone 
Free Testosterone 

Estrogen Effect in Gonadal Men

- Estradiol is known to suppress testosterone through gonadotropin inhibition
 - However, transgender males do not have testes
- In the presence of testosterone (in natal males) elevations in estrogens do not appear to be harmful (signs of androgen deficiency or impairment of sexual function)
- Effect of estrogen administration on non-natal males patients taking testosterone is not known



Summary of Treatment

- Increase in testosterone dose did not improve vasomotor symptoms in post-oophorectomy/hysterectomy transgender patient
- SNRI was not tolerated in this Patient
- Small dose of estrogen alleviated vasomotor symptoms in this Pt but was short lived
- Twice a week low dose estrogen dosing worked best for improvement of symptoms

Conclusions

- Treatment of hot flashes/vasomotor symptoms after oophorectomy/hysterectomy in transgender patients has not been reported
- VMS from menopause appear to have longer duration in AA women & hormonal treatment is the most effective treatment
- The Endocrine Society has issued recent guidelines to assist providers in the care of transgender individuals
 - Goal of HT in FTM patients is to achieve normal male testosterone levels (400-700ng/dL)
- Treatment with low dose biweekly estrogen improved VMS in an FTM transgender patient on testosterone therapy
- More studies are needed to elucidate the effects of estrogen on transgender patients that are on testosterone therapy (short and long term effects)

References

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Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

- A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender
 4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
 5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)
- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Specify if:
1. The condition exists with a disorder of sex development.
 2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).
-

Reference: American Psychiatric Association (14).

Treatment for Moderate to Severe Hot Flashes

- Nonhormonal: SSRIs, SNRIs, anti epileptics, & centrally acting drugs
 - Venlafaxine (60% reduction at 75mg/d), desvenlafaxine, paroxetine (62% reduction at 12.5mg/d), citalopram (20mg)/d, & escitalopram (NE & 5-HT thought to work in opposite fashion)
 - Side effects: insomnia, sleepiness, dry mouth
 - Clonidine (thought to widen the thermoneutral zone); reduced HF frequency by 46% (PO) & 80% (patch)
 - Side effects hypotension, dry mouth, sedation
 - Gabapentin (unknown mechanism) 45-71% reduction
 - Side effects: somnolence, ataxia, dizziness
- Hormonal therapy is the most effective treatment for HFs; Estrogens alleviate HFs & prevent bone loss associated with menopause
- Estrogen & progestin for women with an intact uterus; Estrogen only for post-hysterectomy
 - SERMs also used with conjugated estrogens as alternative to progestin

Treatment of Gender-Dysphoric Patients Among Endocrinologists

- Recent survey sent to Endocrinologists found that nearly 80% of Endocrinologists have treated a transgender person; However the same percentage reported never receiving formal training
- Study concluded confidence & confidence in transgender health needs to increase among Endocrinologists
- Strategies include online training modules, expansion of formal transgender curricular in fellowship programs & presentations at national & international meetings

Davidge-Pitts, C. et al. J Clin Endocrinol Metab. 2017 Apr;102(4):1286-1290

ES Guidelines on Treatment of Gender-Dysphoric Patients

- Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role
- Clinicians should confirm the diagnostic criteria of GD/gender incongruence before beginning hormonal treatment
- Pts require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex & (2) maintain sex hormone levels within the normal range for the person's affirmed gender
- Clinicians who prescribe gender affirming therapy should be knowledgeable about the diagnostic criteria for gender affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition
- Mental health care should be available before, during and sometimes after transitioning