COMPOUNDED TESTOSTERONE THERAPY IN WOMEN

27 June, 2019
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Outline

- Critical role of testosterone (T)
- Necessity
- Safety and efficacy T implant therapy
- Data on testosterone implants (PK)

Hormone levels (controversies)
The industry
Issues and controversies
   Estradiol pellets, PK studies
“Difference of opinion leads to enquiry, and enquiry to truth; and that, I am sure, is the ultimate and sincere object of us both.”

Thomas Jefferson 1815
BACKGROUND

Critical role of testosterone
Sex drive and libido

‘Low T’
Lean muscle mass, strength, co-ordination, confidence (both sexes)
Androgen Receptors

Every organ system in both sexes
T function at the AR

Every organ system in both sexes
Testosterone (T)

- Most abundant active hormone in both sexes
  
  Direct effect at the androgen receptor (AR)
  
  Peripheral conversion of T is major source of estrogen in men and postmenopausal women
Testosterone > Estradiol levels

Throughout the entire female lifespan

![Graph showing testosterone and estradiol levels over years of age]

Dimitrakakis 02
Adrenal androgens, pro-hormones

Major source of T at the cellular level (75% of T)

**Androstenedione**

*Reference Range*

**Adult Male**
- 18-30 Years: 50-220 ng/dL
- 31-50 Years: 40-190 ng/dL

**Adult Female**
- Follicular: 35-250 ng/dL
- Luteal: 30-235 ng/dL

**DHEA**

*Reference Range*

**Adult Male**
- 61-1636 ng/dL

**Adult Female**
- 102-1185 ng/dL
Androgens decline with age
Testosterone

Peaks in women in their twenties
Gradual decline
Androstenedione (A4)

17B-HSD (T)
Aromatase (E1)
DHEA(S)

3B-HSD (A4) → 17B-HSD (T)
17B-HSD (Adiol) → 3B-HSD (T)
• Serum testosterone is not a valid marker of androgenic activity in women

• ...it is not surprising that despite long series of prospective and case-control cohort studies performed during the last 30 years, a correlation between serum testosterone and any clinical condition believed to be under androgenic control in women has remained elusive.

Controversial guidelines
TRT: Serum T + DHEA(S) + Androstenedione

Endogenous serum T levels (≈ 25%)

DHEA(S) >10 000 x T

Men ≈ Women
30-40% 75% Locally

T at AR

Intra and extracellular AR

Physiologic Effect
Symptoms of androgen deficiency
Men and Women (pre and post menopausal)

- Physical fatigue, exhaustion
- Bone loss
- Muscle wasting
- Fat accumulation
- Thin, dry skin, wrinkles, brittle hair and nails
- Chronic pain, muscle aches, stiffness
Symptoms of androgen deficiency

- Urinary incontinence, frequency, urgency
- BPH
- Vaginal atrophy
- Decreased sex drive and libido
- Impotence (decreased performance)
Symptoms of androgen deficiency

- Dysphoric mood
  - Depression, anxiety, irritability, loss of confidence
- Sleep disturbance, insomnia
- Vasomotor instability (hot flashes)
- Cognitive changes, decreased mental focus
- Memory loss
- Increased inflammation
Age associated diseases, T beneficial effect

- Obesity
- Coronary artery disease, CHF
- Pulmonary disease, asthma, COPD
- Insulin resistance, diabetes, metabolic syndrome
- Cancer (immune function)
- Neurological diseases, dementia
- Osteoporosis, sarcopenia
NECESSITY

There is no FDA approved USP testosterone product for women in the United States
Compounded vaginal cream

Testosterone with estriol (E3)
Testosterone, estriol, and progesterone
Testosterone (± P)

- Initially began using in breast cancer patients for urogenital symptoms over 20 years ago
- Non BCA patients
- Vaginal dryness, urinary urgency, frequency, painful sex, etc.
- Systemic symptoms

DATA
USP Estriol (E3)

- Low binding affinity for myometrium and breast
- High binding affinity in bladder and vagina
- Vaginal estriol does not increase the risk or recurrence of breast cancer
- Does not accumulate
- OTC in Europe
- Only available in compounded preparations in the US

Lack of data on the efficacy of topical estriol (skin)
# Affordable care

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<th>Dosing</th>
<th>Cost per month</th>
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<td>$22.10</td>
<td>1 daily for 2 weeks then twice weekly</td>
<td>$176.86 ($397.80 1st month)</td>
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<td>Generic vaginal estradiol</td>
<td>$146.33</td>
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<td>$63.06- $146.33 ($329.22 1st month)</td>
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<td>Intrarosa® Vaginal DHEA 6.5 mg</td>
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<td>Compounded Vaginal DHEA cream 20 mg/gm</td>
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<td>$18.76 28d</td>
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<tr>
<td></td>
<td>30 grams</td>
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<tr>
<td>Compounded T + Estriol Cream</td>
<td>$40.95*</td>
<td>120</td>
<td>$0.34</td>
<td>0.25 g daily for 14 d then 2-3 times weekly</td>
<td>$4.08 if 3x weekly $10.20 if daily</td>
</tr>
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</table>
Compounded T pellets, 80 years

1937 US both sexes
- Therapy for BCA
- Compressed T powder
- 1972 FDA approved 75 mg T pellet, Testopel®
- 50, 100, and 200 mg T pellets
  Europe and Australia
- Implants used in women (US) are compounded

Compounded formulations
  T + Anastrozole (AI)
  T + Finasteride
implantation of hard compressed pellets of crystalline steroids resulted in a slow and more physiologic absorption of the hormone.

“...endogenous mechanism of hormonal secretion is more nearly approached and the physiologic action of the hormone more closely imitated.”
Indications for T pellets - 70 years

- Menopausal symptoms in whom estrogen therapy has proved unsatisfactory or is contraindicated
- Prevent uterine bleeding
- Endometriosis
- Fibroids
- Nocturia
- Low libido
- Carcinoma of the breast
- Addison’s disease
- Anorexia
Breast cancer patients

• It would be impossible to adequately treat breast cancer survivors without compounded formulations
  Compounded vaginal testosterone + estriol cream + progesterone
• T + anastrozole (an aromatase inhibitor) combination implant (2009)
• DATA presented at ASCO 2010

‘The combination of testosterone with anastrozole, delivered subcutaneously, provides therapeutic levels of testosterone without elevating estradiol levels’.
Testosterone $\rightarrow$ Estradiol

Aromatase

Breast Cell

↓ proliferation

↑ proliferation
Testosterone (T) and estradiol (E2) levels over time

Days since insertion of T + A implant

T levels

E2 levels

$R^2 = 0.0044$
Efficacy of subcutaneous T on symptoms in BCA patients

Validated QoL questionnaire (MRS)

Prospective study

BCA patients (Stage 0-4)

Compounded Testosterone + Anastrozole (A) implants

Documented therapeutic T levels on therapy

ASCO 2014

- No ADE
- No disease recurrence

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (y)</td>
<td>50.04 ± 10.66 (31.25-90.26)</td>
</tr>
<tr>
<td>Age at first insertion (y)</td>
<td>57.17 ± 10.51 (31.74-90.28)</td>
</tr>
<tr>
<td>Treatment years</td>
<td>3.93 ± 2.41 (0.11-8.37)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.03 ± 4.69</td>
</tr>
<tr>
<td>Testosterone dose (mg)</td>
<td>168.89 ± 32.25</td>
</tr>
<tr>
<td>Anastrozole dose (mg) (n)</td>
<td>4 (5), 8 (66), 12 (1)</td>
</tr>
<tr>
<td>Testosterone level (ng/dl)</td>
<td>354.42 ± 149.06</td>
</tr>
<tr>
<td>Stage-0, 1, 2, 3, 4 (n)</td>
<td>15, 25, 23, 6, 3</td>
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<tr>
<td>Disease recurrence (n)</td>
<td>0</td>
</tr>
<tr>
<td>Disease progression (n)</td>
<td>1</td>
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</table>
Quality of Life
### Symptoms:

**60 yo metastatic BCA 5/2015**

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<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
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<tbody>
<tr>
<td>1. Hot flashes, sweating (episodes of sweating)</td>
<td>☑️</td>
<td>☐️</td>
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<td>4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)</td>
<td>☑️</td>
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<td>6. Anxiety (inner restlessness, feeling panicky)</td>
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<td>☐️</td>
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<td>7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)</td>
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<td>8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)</td>
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<td>☑️</td>
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On T + L implant therapy 11/2017  
(Off Vicodin, Ativan, Ambien)
Quality of life

3.5 years T + L

Thriving

Compounded implants:
T 240 mg + Letrozole 12 mg
Finasteride 6 mg
Survival

- This patient wouldn’t be alive....
Therapy for breast cancer

82 y.o. patient (180 mg T + 12 mg A)

31 May 2013 (3.7 cm)  25 July 2013 (2.0 cm)
19 weeks

31 May 2013

October 2013
T + Letrozole implant
Side effects from chemotherapy

51 yo female diagnosed with 3.3 cm IDC
To receive pre-op chemotherapy
Testosterone (180 mg) + Letrozole (8 mg) implants
- 43% reduction in tumor at day 41, prior to starting CTX
- Complete pathological response
- No long term effects (cardiac or neurological) from CTX

Cost

$230 includes office visit, insertion procedure, review labs, and medical care for 3 months.

<table>
<thead>
<tr>
<th>Service</th>
<th>Amount billed</th>
<th>Amount covered by insurance</th>
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<tbody>
<tr>
<td>T + AI implant</td>
<td>230^a</td>
<td>0^b</td>
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<tr>
<td>Chemotherapy (six cycles)</td>
<td>125,000</td>
<td>60,600</td>
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<tr>
<td>Six additional trastuzumab</td>
<td>46,500 (7,750 × 6)</td>
<td>22,590 (3,765 × 6)</td>
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<tr>
<td>Pegfilgrastim</td>
<td>46,200 (7,700 × 6)</td>
<td>23,400 (3,900 × 6)</td>
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<tr>
<td>Two-day hospital charge</td>
<td>71,000</td>
<td>61,420</td>
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<tr>
<td>Additional expenses^c (estimate)</td>
<td>45,000</td>
<td>25,000</td>
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</table>
RESEARCH & DATA

Efficacy and safety
In vitro dissolution studies

Accelerated dissolution in oil, 134°F

- Testopel
- T 110 mg
- T 85 mg
- T 60 + A 4
Efficacy in women


Testosterone implants alone (no estrogen)
N=300
  108 premenopausal (35.3%)
Indications: T implants N=300 women, pre and post meno

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<tr>
<th>Symptoms</th>
<th>none</th>
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<th>extremely</th>
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Score = 0 1 2 3 4
Migraine headaches-testosterone implants


<table>
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<tr>
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<th>Combined cohort</th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
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<tr>
<td></td>
<td>N = 27</td>
<td>N = 16</td>
<td>N = 11</td>
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<tr>
<td>Mean age</td>
<td>47.4 ± 9.6 years</td>
<td>41.8 ± 5.5 years</td>
<td>55.5 ± 8.7 years</td>
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<tr>
<td>Mean severity score a at baseline</td>
<td>3.63 ± 0.55</td>
<td>3.72 ± 0.52</td>
<td>3.5 ± 0.59</td>
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<tr>
<td>Mean severity score a on therapy</td>
<td>0.37 ± 1.08</td>
<td>0.63 ± 1.36</td>
<td>0b ± 0</td>
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<tr>
<td>Absolute change c in severity score</td>
<td>3.26 ± 1.19</td>
<td>3.1 ± 1.46</td>
<td>3.5 ± 0.59</td>
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<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</table>
Voice changes

Prospectively followed 10 women treated with T pellet implants for one year
Mean T pellet dose 138.0 ± 22.7 mg
Measured fundamental frequencies at baseline, 3, 6, and 12 months
No change in fundamental frequency among subjects

FACT: There is no evidence that SQ testosterone therapy causes hoarseness or irreversible vocal cord changes in women

T is not excreted in breast milk

Testosterone, delivered by a subcutaneous pellet implant was effective in relieving symptoms of testosterone deficiency and was not measurably increased in breast milk or measurable in infant serum.

International Congress on Steroidal Hormones and Hormones & Cancer, Quebec City, Canada (September 2008)
Long term safety T implants


Over 60% reduction in the incidence of breast cancer
Safety of higher ‘male’ doses of T

- 500-1800 mg doses of T used to treat BCA patient
- Supra-physiologic doses in female to male transgender patients have been demonstrated to be safe
Research: Alliance cancer trial A221102

- National double-blind randomized trial
- **Compounded** combination T + A pellets
- **Compounded** topical cream
- Results under publication

Pharmacokinetic studies


Safety and efficacy of current T doses

Therapeutic levels on therapy

Controversial ES guideline recommendation (not based on evidence)

“… resulting in a mid-normal premenopausal value in a reference assay to avoid pharmacological T administration.”
Pharmacologic dosing for a physiologic effect

Female study T implants

- Dose $133.3 \pm 26.8$ mg, range 55-240 mg
- Results
  - Week 4 levels (n=154), $300 \pm 107$ ng/dl
    - 4-6 x endogenous range, 44/72 ng/dl
  - Symptoms returned (n=261), $171 \pm 73$ ng/dl
    - 2-3 x endogenous range
      - Subset: Quest lab (n=154)
        - TT $185$ ng/dl (2-45 ng/dl), fT $19$ pg/ml (0.1-6.4 pg/ml)

No ADE

Basic physiology

3B-HSD (A4) → 17B-HSD (T)
17B-HSD (Adiol) → 3B-HSD (T)
T replacement at the end organ (cellular level)
Serum T + DHEA(S) + Androstenedione

Endogenous serum T levels (≈ 25%)

DHEA(S)
>10,000 x T

Men ≈ Women
30-40% 75% Locally

Intra and extracellular AR

T at AR

Physiologic Effect

T > 5 x T
Data

• Levels on therapy apply only to the SQ implant
• Basic physiology
  Serum T levels reflect the contribution of androgen precursors to T available at the end organ

FACT: Symptoms returned T levels 171 ± 73 ng/dl
  TT 185 ng/dl (2-45 ng/dl), fT 19 pg/ml (0.1-6.4 pg/ml)

FACT: NO ADE in over 10-years of therapy
Male data on compounded implants

  SC T + A implant therapy does not increase and may lower the occurrence of venous thrombotic events.

- Subcutaneous **Testosterone Anastrozole** Therapy in Men: Rationale, Dosing, and Levels on Therapy (Under publication IJPC 2019)
  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.
Myths and misconceptions


There is no data…. The biggest myth of all
CONCLUSION

Compounded testosterone use in women 2019
Conclusion

• T is critical for health, and well-being

• The gradual decline of T associated with aging is responsible for many of the adverse signs and symptoms of aging including mental and physical deterioration

• TRT must be done with adequate doses
  Clinical effect (benefits) vs. adverse events (risks)
  -Not serum levels on therapy
Compounded hormones

- Compounded hormones are critical to the care of millions of breast cancer patients in whom estrogen therapy is contraindicated
- Compounded T + AI (anastrozole/letrozole) implants have been shown to treat breast cancers and improve QoL in breast cancer survivors
  - Maintain therapeutic T levels without raising estradiol levels
- Compounded T + A implants prevent side effects of excess estrogen in male and female patients
Compounded testosterone

- Compounded testosterone implants have been safely used in women for over 80 years
- Subcutaneous testosterone is clinically effective
- Data exists on the safety, efficacy, and pharmacokinetics of compounded subcutaneous testosterone implants
- There is a demand (over 80 years)
- **Supply:** FDA approval in women????
- There will still be a need for compounding!
  - Dosing
  - Inactive ingredients
  - Combination formulations
The Art of Medicine
HORMONE LEVELS
To measure or not to measure
Critics of compounded BHRT

• Under-dosing or overdosing
  Can occur with compounded BHRT or conventional HT

• Measuring levels on therapy is controversial
  Ranges on (T) therapy are controversial but data supports efficacy and safety

• Equivalence studies
  No two patients absorb, distribute, metabolize, or excrete any medication the same
Clinical decision vs. labs

Hormone levels fluctuate and are unreliable.
Standard of care: an individual patient should be treated based on his/her symptoms, response to therapy, as well as the benefits and risks of therapy. An individual’s physical comfort may not be related to their absolute hormone levels.

Known

Testosterone’s effect is dose dependent
Controversy: T levels on therapy (ES)

“Clinicians should maintain serum T levels during treatment in the mid-normal range for healthy young men”.

“… resulting in a mid-normal premenopausal value in a reference assay to avoid pharmacological T administration.”

NO EVIDENCE that this is effective therapy or that higher levels are associated with ADE

Do not specify method of delivery
The data disagrees

Physiology disagrees
Clinically effect dose, No ADE

<table>
<thead>
<tr>
<th>Year published</th>
<th>Study</th>
<th>Mean T dose mg.</th>
<th>Mean serum T ng/dL</th>
</tr>
</thead>
<tbody>
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<td>2013</td>
<td>PK</td>
<td>133.3 ± 26.8</td>
<td>300 ± 107</td>
</tr>
<tr>
<td></td>
<td>N=154 (4 week)</td>
<td></td>
<td>171 ± 73</td>
</tr>
<tr>
<td></td>
<td>N=261 (end)</td>
<td></td>
<td></td>
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<tr>
<td>2014</td>
<td>Breast Cancer</td>
<td>168.9 ± 32.2</td>
<td>354 ± 149</td>
</tr>
<tr>
<td></td>
<td>N=73</td>
<td></td>
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<tr>
<td>2016</td>
<td>Voice Study</td>
<td>138.0 ± 22.7</td>
<td>472 ± 148</td>
</tr>
<tr>
<td></td>
<td>N=10</td>
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</table>
Weight/BMI and levels on therapy
Week 1 levels women (preliminary data), Male data

- Levels on therapy affected by weight/BMI
- Women < 130 pounds have higher levels on therapy despite lower (weight based) dosing
  - Wt < 130 $542.3 \pm 223.7$ ng/dl (mean dose 165 mg)
  - Wt > 160 $452.5 \pm 192.5$ ng/dl (mean dose 213 mg)

- Similar results in male patients (under publication IJPC)
  The mean T level when symptoms return in men with a BMI <25 is $650.5$ ng/dl compared to $586.4$ (BMI 25-<30), $567.9$ ng/dl (BMI 30-<35), and $514.7$ ng/dl (BMI $\geq$35).
  Midrange when symptoms return
Micromanaging T levels

- Reliability
- Inter-individual variation
- Intra-individual variation

Therapy should be based on clinical effect and therapeutic response (benefits) vs. side effects (risks)

Inadequate doses are ineffective
Inter-individual variation

Week 4 serum T levels, 100 mg T implant  N=12

Mean T level 190.8 ± 80 ng/dl (range 83-368, CV 41.9%)  Zava, Glaser
Mean 39.3 ± 17.2 pg/ml (range 17-86, CV 43.8%). Ref. 20-50 pg/ml (Zava, Glaser)
**Intra-individual variation**

Single female patient tested over 26 h

Venous blood spot T levels, 112.5 mg T implant

Mean T level $268.4 \pm 67.1$ ng/dl (range $176-383$, CV 25%) Zava, Glaser
Hormone level testing

- (However) individualized testing in only indicated when a narrow therapeutic window exists for a drug or drug class
- Steroid hormones… do not meet these criteria and thus do not require individualized testing.
ACOG Hormone level testing cont.

• If treatment is initiated for symptom control, subjective improvement in symptoms is the therapeutic end point, and there is no need to assess hormone levels.

• Hormone therapy should not be titrated to hormone levels.

AGREED!
Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement JCEM 2016

... there is no evidence that monitoring compounded HT with serial salivary or blood testing is effective, except in the case of thyroid hormone.
We continue to recommend against making a diagnosis of androgen deficiency syndrome in healthy women because there is a lack of a well-defined syndrome, and data correlating androgen levels with specific signs or symptoms are unavailable.

**Versus**

...recommend that HT be individualized on the basis of symptoms (not hormone levels)

*Idiom* - Speaking/maintaining contradictory positions or beliefs, often self-serving
• Serum testosterone is not a valid marker of androgenic activity in women
• ...it is not surprising that despite long series of prospective and case-control cohort studies performed during the last 30 years, a correlation between serum testosterone and any clinical condition believed to be under androgenic control in women has remained elusive.
Recommend testing for T

• 5.2 If a woman is to be given a trial of T therapy, we suggest checking baseline T level and the use of an approved non-oral preparation for women (such as a transdermal patch, gel, or cream) if such a treatment is available.

• 5.3 We suggest monitoring T levels 3–6 weeks after initiation of therapy and every 6 months thereafter to assess for patient overuse or signs of androgen excess.

No evidence
Confused???

• ...baseline hormone measurements to replace “abnormal” hormone deficiencies has no basis in medical practice.

• ...HT be individualized on the basis of symptoms (not hormone levels) for menopausal women using HT with estrogen and/or progestin, or androgen.
Convictions are more dangerous enemies of truths than lies.

Friedrich Nietzsche
THE INDUSTRY

Specialty societies and COI
<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost Details</th>
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<tr>
<td><strong>Testopel®</strong> 75 mg pellet</td>
<td>$92.30 per 75 mg pellet *92.30</td>
</tr>
<tr>
<td></td>
<td>$2215.20 for 1800 mg dose (male)</td>
</tr>
<tr>
<td></td>
<td>$18.46/day based on 120 d cycle</td>
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<tr>
<td>Compounded Testosterone pellet</td>
<td>$15 per 100 mg pellet</td>
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<tr>
<td></td>
<td>$270 for 1800 mg dose (male)</td>
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<tr>
<td></td>
<td>$0.50/day female 90 d cycle</td>
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<tr>
<td></td>
<td>88% less</td>
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<tr>
<td><strong>Androgel®</strong> 88 g of 1.6%</td>
<td>$625 vs. Generic $241.25 (coupon)</td>
</tr>
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<td></td>
<td>40.5 mg/2 pumps in 5.0 g gel</td>
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<tr>
<td></td>
<td>$20.85/d</td>
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<td>$8.04/d generic</td>
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<tr>
<td>Compounded Testosterone gel Or cream WIP</td>
<td>Gel 40 mg/g $72/30 d</td>
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<tr>
<td></td>
<td>Cream 160 mg/g $35/30 d</td>
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<td>80 mg dose</td>
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<tr>
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<td>0.5 g per day</td>
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<tr>
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<td>80 mg dose 0.5 g per day</td>
</tr>
<tr>
<td></td>
<td>70% less than generic</td>
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<tr>
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<td>85% less than generic</td>
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<td>&gt;95% AndroG</td>
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<td><strong>Bijuva®</strong> Oral capsule E2/P</td>
<td>$238.98 one month (#30) $7.96</td>
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<td>One per day</td>
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<td>$7.96</td>
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<tr>
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<td>$39.60 (#30) $1.32 (#30) $1.14 (#90)</td>
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<td>One per day</td>
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<td>$1.14-1.31</td>
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<td>85% less</td>
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<tr>
<td><strong>Estrogel®</strong> Topical E2 gel</td>
<td>$106.88-149.95 per 50 gram bottle $3.00/gram without coupon</td>
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<td></td>
<td>1.25 gm/pump* (0.75 mg E2) 2 pumps per day</td>
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<tr>
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<td>≈ $3.75/1 pump $7.50 for 1.5 mg E2 (2 pumps)</td>
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<tr>
<td>Compounded Topical E2 gel WIP</td>
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<td>1 to 1.5 gram depending on mg E2/gm gel</td>
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<td>$1.00 - $1.50</td>
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<td>Over 50-80% less</td>
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Specialty societies (funded)

ES, NAMS, ACOG, IMS

• Opinions
• Guidelines
• Journals
• COI
• KOL
• Meetings
• Presentations
Competition

• Most articles, guidelines, and opinions expressing concern over compounded BHRT are sponsored by pharmaceutical companies (specialty societies)
• Published in ‘Society’ Journals
• Physician authors with COI
• Ghost authors or paid marketing authors (e.g. Precise publications, LLC)
Disclosure Summary: N.S. received grant support from Bayer, Inc and stock options from Menogenix; G.D.B. worked on the editorial staff at Merck, participated in a mock Food and Drug Administration meeting with Amgen, and worked as a consultant at Allergan; C.L.B. was employed at Biogen; K.A.M. and M.M. has nothing to declare; and J.V.P. received consultant fees from Pfizer, Noven Pharmaceuticals, Novo Nordisk, TherapeuticsMD, and Shionogi (paid directly to the University of Virginia), and received research grants from TherapeuticsMD and Endoceutics (paid directly to the University of Virginia).
2013 The following JCEM Editors reported relevant financial relationships:

The Editor-in-Chief, Leonard Wartofsky, M.D., is a Consultant for Asurogen, Genzyme, and IBSA, and is on the Speaker's Bureau for Genzyme. Kenneth Burman, M.D., is a Consultant for Medscape and UpToDate; a Reviewer for the Endocrine Fellows Foundation; and has received Institutional Grants for Research from Amgen, Eisei, and Pfizer. Samuel Dagogo-Jack, M.D., is a Consultant for Merck and Novo Nordisk; a Grantee for the American Diabetes Association, AstraZeneca, Boehringer Ingelheim, National Institutes of Health, and Novo Nordisk; and a Grant Reviewer for the American Diabetes Association and National Institutes of Health. Silvio Inzucchi, M.D., is a Consultant/Advisor for Boehringer Ingelheim, Genentech, Janssen, Merck, and Takeda; has DSMB Activity with Amgen, Esai, and Gilead; and receives CME support from Abbott, Amylin, Boeringher-Ingelheim, Merck, and Takeda. Kieren Mather, M.D., received an Investigator-initiated Grant from Novo Nordisk. Lynnette Nieman, M.D., is an Author/Editor for UpToDate, and receives Research Support from HRA-Pharmaceutical.
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- Pfizer, Inc.
- Sandoz
- Sanofi
- Shire International GmbH
- Therapeutics MD, Inc.
‘Classic faux-advocacy’

- The Hormone Health Network offers a variety of programs and services to reach the public with important hormone-related information. Its strategies involve dissemination and promotion directly to consumers, physicians and consumer media. HHN welcomes the opportunity to collaborate with corporations, patient support groups, government agencies, and non-profit organizations to expand the reach of important health messages in creative ways.
Articles

Funding/support: TherapeuticsMD sponsored the study and provided support for final manuscript editing by Dominique Verlaan, PhD, CMPP (Precise Publications, LLC).

Financial disclosure/conflicts of interest: Dr Stanczyk consults for Agile Therapeutics, Mithra, and TherapeuticsMD. Chunying Niu has no conflicts of interest. Colleen Azen consults for TherapeuticsMD. Dr Mirkin is an employee of TherapeuticsMD with stock/stock options. Ms Amadio is an employee of TherapeuticsMD with stock/stock options.

2019 by The North American Menopause Society (Menopause)
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Clinical Practice Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient’s individual circumstances.
COMPOUNDING BHRT
Issues and controversies
Compounding

- False claims of superiority, proprietary pellets
- Some pharmacies compound formulations without testing
  Anastrozole alone implant
- Omit autoclaving pellet, which heat fuses the implant and slows release. BUT, this has been dictated by some state boards of pharmacy.
  Have not done dissolution testing
  Gamma radiation may be acceptable
  The FDA approved pellet is autoclaved and the process has worked for over 80 years.
Testing omitted

Dissolution in oil

Weight of implant in mg

Time in minutes, T raised at 180 minutes from 156 to 196 degrees F

- TP 79 mg
- T+L 10:1
- TP 79 old
- Letrozole
Against the **routine** use of estradiol pellets

- Not a compounding issue
- Physician decision
- Not needed
- T is the major source of estradiol at the cellular level
- Continuous T provides adequate estradiol in the majority of women
- Complications
Estradiol pellet

- Estradiol can accumulate
- Prolonged stimulation of the uterine lining (prolonged bleeding)
- Increased risk of breast with higher doses
  Not removable (Treat with Tamoxifen)
- No evidence to support dosing to suppress FSH
- No evidence to support ‘minimum’ serum levels of E2

- Most physicians prescribe lower doses of E2 (6-15 mg)
  Limited data, safer
- Estra pellet FDA approved for shipping overseas
Data does exist (Studd 94)

<table>
<thead>
<tr>
<th></th>
<th>Oestradiol implants</th>
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<tr>
<td></td>
<td>25 mg</td>
<td>50 mg</td>
<td>75 mg</td>
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<tr>
<td>Oestradiol (pmol/l)</td>
<td>327 (114–853)</td>
<td>358 (220–957)</td>
<td>518 (167–828)</td>
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<tr>
<td>FSH (iu/l)</td>
<td>26.8 (2–66)</td>
<td>11.6 (1.1–28)</td>
<td>5.55 (0.9–33.7)</td>
</tr>
</tbody>
</table>
References

PK compounded estradiol implants


Comparison-equivalence

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<tr>
<th>Formulation</th>
<th>Dose (mg)</th>
<th>Serum level (pg/ml)</th>
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<tbody>
<tr>
<td>CEE</td>
<td>0.625</td>
<td>40</td>
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<tr>
<td></td>
<td>1.25</td>
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</tr>
<tr>
<td>Micronized estradiol</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>Transdermal estradiol patch</td>
<td>0.05</td>
<td>25-40</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>60</td>
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<tr>
<td>Estradiol gel</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Estradiol implant</td>
<td>25</td>
<td>89</td>
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</table>

Estrogen formulations and serum levels
Randomized trial

- Compounded OMP 100 mg vs. Prometrium (100 mg)
  Serum progesterone levels were comparable in conventional vs. compounded groups
  Prometrium #30, $328.88 with coupon
  Generic #30, $22.75 with coupon
  Compounded #30, $39.50

- Topical BiEst, estradiol levels were not equivalent to the patch

Critics of cBHRT

- **Under-dosing or overdosing**
  Can occur with compounded BHRT or conventional HT

- **Measuring levels on therapy is controversial**
  Ranges on (T) therapy are controversial but data supports efficacy and safety

- **Equivalence**
  No two patients absorb, distribute, metabolize, or excrete any medication the same

Standard of care: an individual patient should be treated based on his/her symptoms, response to therapy, as well as the benefits and risks of therapy
BHRT ‘movement’

- Popularity
- Marketing
- Hype and claims
- Micromanaging dosing based on repetitive testing
  - No data
- Self appointed experts and their methodology
  - Data often only case presentations
  - Unsubstantiated claims of superiority
  - Unsubstantiated criticism of other therapies (blogs etc.)
- Lack of data on some preparations
  - Safety is not an issue (excluding higher doses of estradiol)
Separate ‘compounding’ from ‘BHRT movement’

Ideology is here to stay

  Individualized therapy
  Listening to the patient
  Bio-similar formulations (advantage)

There will always be a need for compounded BHRT
You have your way.
I have my way.
As for the right way, the correct way, and the only way, it does not exist.

Friedrich Nietzsche