Applying SERMS to Advance the Management of Menopause

Lila Nachtigall, MD NCMP
Professor of Ob/Gyn
NYU School of Medicine
Disclosures

I have nothing to disclose
SERMs

- Selective
- Estrogen
- Receptor
- Modulators
The Dynamics of Estrogen & Estrogen Receptors

- Estrogen regulates the growth, development, and physiology of the reproductive system.
- The biological functions of estrogen are mediated by binding to Estrogen Receptors (ER) which are found in most of the female body’s tissues.
- In each target tissue the ERs have specific characteristics, providing a certain response within the tissue.
Short & Long-Term Effect of Hormone Depletion

- ERs are found in most of the female body’s tissues
- Estrogen decline affects all tissues

- Tremendous impact on short & long term QoL of women
Effect of estrogen depletion in the Brain & Nervous System

- Estrogen affects the autonomic control, the emotional state, and higher brain functions;
- Reduction in estrogen levels leads to:
  - Mood swings
  - Memory loss
  - Problems focusing
  - Irritability
  - Fatigue
  - Hot flashes & night sweats
  - Stress & Anxiety
  - Depression
  - Decreased libido
KNDy Neurons

- Kisspeptin: G-protein coupled receptor ligand neuropeptide (gene kiss1)
- Neurokinin B: endogenous peptide ligand that belongs to the family of tachykinin peptides (gene TAC) highest affinity NK3R
- Dynorphin: kappa opioid
- KNDy neurons are co-localized with > 95% of ER, PR, AR in arcuate nucleus

Szeliga A, Gennazzani AD. Gynecological Endocrinology, 34:11, 913-919, DOI: 10.1080/09513590.2018.1480711
WORKING HYPOTHESIS

Szeliga A, Gennazzani AD Gynecological Endocrinology, 34:11, 913-919, DOI: 10.1080/09513590.2018.1480711
The Need
Symptoms/Time Line

The decline in estrogen levels in women leads to a **chronic hormonal imbalance** which accompanies women their 40’s onwards.

### Primary stages of estrogen decline - Peri Menopause
- Irregular periods
- Decreased energy levels
- Anxiety
- Irritability
- Sleep disturbance
- Fatigue
- Skin dryness
- Wrinkles
- Mood changes

### Menopause
- Hot flashes
- Night sweats
- Palpitations
- Joint & Muscle pain
- Fatigue
- Anxiety
- Feeling of loss & loneliness
- Irritability
- Insomnia
- Loss of libido
- Bone loss - Osteopenia

### Post-menopause
- Vaginal atrophy
  - painful intercourse
  - increased vaginal infections
- Increased UTI
- Osteoporosis
- Joint & muscle pain
- Depression
- Insomnia
- Fatigue
- CVD

The decline in estrogen levels in women leads to a **chronic hormonal imbalance** which accompanies women their 40’s onwards.
## Symptoms vs. Conditions/Disease

### Symptoms
- Mood swings - *Brain*
- Irritability - *Brain*
- Sleep disturbance - *Brain*
- Hot flashes & night sweats - *Brain*
- Problems focusing - *Brain*
- Painful intercourse - *Reproductive Tract*

### Conditions
- Osteoporosis & fractures - *Bone*
- CVD - *Heart*
- Recurrent UTI - *Urinary tract*
- Heightened stress, anxiety & depression - *Brain*
- Recurrent VTI - *Reproductive Tract*
- Vaginal Atrophy - *Reproductive Tract*
- Depression - *Brain*
- Fatigue - *Brain*
- Decreased libido - *Brain*

### Conditions that have high impact on women’s self perception
- Skin aging - *Skin*
- Weight gain and change in fat distribution - *Metabolism*
The 50+ Woman

• Are aware that they have no periods = menopause
• More recognized symptoms: Hot flashes & Night sweats
• No awareness that other symptoms relate to estrogen decline:
  — Fatigue
  — Anxiety
  — Feeling of loss & loneliness
  — Irritability
  — Insomnia
  — **Loss of libido** - which brings great distress
• We need to increase awareness about all aspects of estrogen loss
The 60 + woman

No more hot flashes for the majority

• However, it is important to support many other aspects:
  – Vaginal health- from atrophy to sexual health
  – Recurrent vaginal infections
  – Recurrent UTIs
  – Detain the bone loss process and development of osteoporosis
  – Joint & muscle pain
  – Depression
  – Insomnia
  – Lower energy levels & fatigue
The Ultimate Treatment Path

- Needs to target ER- as this is key in providing healthy aging
- We do not want to target all ER- as this increases risks in tissues that relate to reproduction
- We need a product with SERM properties targeting the desired tissues while not affecting the sensitive tissues

Ideal Treatment - SERM Properties

- Hot flashes
- Night sweats
- Breast cancer
- Endometrial cancer
- Osteoporosis
- Mood & energy levels
- Cardiovascular protection
- No risk of clotting -
  - Strokes
  - Deep Vein Thrombosis
Prevalence of Menopause in the US

- In the United States, approximately 1.3 million women become menopausal each year.
- It typically begins between the ages of 51 and 52.
- However, about 5% of women experience early menopause between the ages of 40 and 45.
- Additionally, 1% of women experience premature menopause before the age of 40, due to permanent ovarian failure that may be associated with sex chromosome abnormalities.
- In 2020 the number of US women older than age 51 is expected to be more than 50 million.*

Treatment of Estrogen Decline

• From temporary symptoms to the development of diseases
• Women’s Quality of Life is greatly affected
• HT provides a worthy solution, however, it has many limitations:
  – Its use is not recommended for the long-term
  – Today, many women and many physicians avoid the use of HT
  – Time consuming to persuade adherence
  – Many contraindications
The Estrogen Receptor

17β-estradiol

SERM

Relative Binding Affinity

<table>
<thead>
<tr>
<th></th>
<th>ER-α</th>
<th>ER-β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Genistein</td>
<td>5</td>
<td>36</td>
</tr>
</tbody>
</table>

Treatment of Estrogen Decline

- From temporary symptoms to the development of diseases
- Women’s Quality of Life is greatly affected
- HT provides a worthy solution, however, it has many limitations:
  - Its use is not recommended for the long-term
  - Today, many women and many physicians avoid the use of HT
  - Time consuming to persuade adherence
  - Many contraindications
The Ideal SERM

• Decrease hot flushes
  • Increase bone density
  • Prevent fractures in spine and hip
  • Prevent breast cancer
  • Improve cardiovascular health
  • Lubricate the vagina
  • No effect on the endometrium

Clinical Trial Overview: Double-Blind, Placebo Controlled Trial


“[Relizen], a herbal remedy made from pollen extracts, reduces hot flushes and improves quality of life in menopausal women: a randomized, placebo-controlled, parallel study”

- **Study Type:** Randomized, Double-Blind, Placebo-Controlled Trial
- **Structure:**
  - 64 menopausal women took two tablets of product (320mg) or placebo daily for 3 months; 54 women completed the study
  - Patients evaluated 16 symptoms on the Menopause Rating Scale at study visits (Days 0, 30, 60, 90)
  - Participants recorded symptoms in a daily diary and rated severity of each symptom
  - 3-month open-label extension offered to all patients taking product daily, with all women (26 women) opting to participate
- **Clinical endpoints:** Frequency of hot flashes, quality of life indicators based on the Menopause Rating Scale (MRS)
Does Bee Pollen reduce vasomotor symptoms compared to placebo?

— Relizen significantly reduced the number of reported hot flashes vs. placebo —

- Compared to the placebo group, patients in the treated group experienced a 30.8% greater decline in the number of hot flashes after three months of treatment ($p < 0.026$)

- Patients in the treated group experienced statistically significant improvement compared to baseline at 2 months ($p < 0.021$) and a further reduction at 3 months ($p < 0.001$)

- Using the Menopause Rating Scale (MRS), another way that hot flashes were assessed, women taking Bee pollen extract reported a decrease in hot flashes that was superior to placebo at Month 2 ($p < 0.027$)

How does Bee Pollen affect other symptoms of menopause?

DBPC results further substantiated in a 400-patient open-label trial

- Change in Menopause Symptoms from Baseline after 12 Weeks of Relizen Use

<table>
<thead>
<tr>
<th>Hot Flash Frequency</th>
<th>Hot Flash Intensity</th>
<th>Night Sweats Frequency</th>
<th>Night Sweats Intensity</th>
<th>Fatigue</th>
<th>Irritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>-65%</td>
<td>-64%</td>
<td>-66%</td>
<td>-67%</td>
<td>-51%</td>
<td>-54%</td>
</tr>
</tbody>
</table>

N = 417 (373 completed)

- P = 0.0659
- P = 0.0003
- P < 0.0001
- P < 0.0001
- P < 0.0001
- P < 0.0001

Bee Pollen also improved patients’ quality of life:

- 47% of patients experienced improvements in quality of sleep (p < 0.0001)
- 48% of patients experienced improvements in quality of life (p = 0.0009)

DT56a, a Botanical Therapy with SERM Properties

- DT56a, is a standardized substance from soybeans produced under strict pharmaceutical conditions.

- DT56a, is a unique compound that has been modulated to bond to the estrogen receptors without being recognized by the body as estrogen.

- DT56a mimics the structures that are recognized by estrogen receptors as estrogen, bound together with either a co-activator or co-repressor, depending on the tissue forming its SERM properties.

- 20 published studies in leading medical journals.

- 19 years of market exposure  
  – 8 Million Months of Treatment
The Basic Biochemistry Behind DT56a

- DT56a mimics the attachment of $E_2$ to the ER in a selective manner forming a phyto-SERM (Selective Estrogen Receptor Modulator from botanical source)
Effect of DT56a vs. HT & Control Clinical Study

- Femarelle decreased menopausal symptoms significantly and in the same degree as Activelle ($p<0.001$)

<table>
<thead>
<tr>
<th>Factor Examined</th>
<th>No treatment (n=36)</th>
<th>HT (n=26)</th>
<th>DT56a (n=27)</th>
<th>ANCOVA P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupperman scoring</td>
<td>Baseline</td>
<td>10.62 (8.265)</td>
<td>8.82 (6.840)</td>
<td>13.64 (3.613)</td>
</tr>
<tr>
<td></td>
<td>Final</td>
<td>9.96 (5.853)</td>
<td>3.35 (4.506)</td>
<td>9.63 (8.357)</td>
</tr>
<tr>
<td></td>
<td>P^b</td>
<td>0.207</td>
<td>0.032</td>
<td>0.001</td>
</tr>
<tr>
<td>Hot flushes/night sweats</td>
<td>Baseline</td>
<td>1.98 (1.73)</td>
<td>2.25 (1.24)</td>
<td>2.17 (0.94)</td>
</tr>
<tr>
<td></td>
<td>Final</td>
<td>2.01 (1.94)</td>
<td>0.25 (0.56)</td>
<td>0.75 (0.69)</td>
</tr>
<tr>
<td></td>
<td>P^b</td>
<td>0.308</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*HT= Hormone therapy *ANOVA = Analysis of variance

(n= 89)
Numerical Reduction of Hot Flashes - DT56a

All Respondents

(Visit 1) Q6: How many hot flashes do you experience on average per day?

(Visit 2) Q2: During the last week, how many hot flashes on average did you experience per day?

86% experienced a reduction of hot flashes, following 4 weeks of treatment

Reduction of Hot flashes compared to Baseline

- Worse: 5%
- No change: 9%
- -1: 14%
- -2: 18%
- -3: 15%
- -4: 12%
- -5 or more: 27%

(n=2,517)
Reduction of Menopausal Symptoms Achieved with DT56a

- Menopausal symptoms were reduced, using DT56a beyond that expected with placebo (placebo = 40%)
  - Frequency ↓ 58%
  - Severity of Hot Flashes ↓ 43%
  - Severity of Night Sweating ↓ 52%
- No increase in endometrial thickness
- No adverse effects observed
- Gonadotropins, SHBG, and DHEAS secretion was unchanged

Nachtigall L NYU Symposium 2012

Effect of DT56a on Menopausal Symptoms
Clinical Study

- No changes in:
  - Endometrial thickness
  - TSH levels
  - Hormonal blood profile

PhytoSerm: Genistein, Daidsein and S Equol

A

Placebo

Initial hot flash frequency

Change in hot flash frequency

r=0.2309
p=0.494

B

PS50

Initial hot flash frequency

Change in hot flash frequency

r=-0.6740
p=0.004

C

PS100

Initial hot flash frequency

Changes in hot flash frequency

r=-0.638
p=0.029
Effect of Estrogen Depletion on the Reproductive Tract

• Monthly menstrual cycle gradually ceases; with this we start to see:
  — Thinning and shrinking of the tissues
  — Decrease in Ph levels and lubrication leading to:
    • Irritation or discomfort during sexual activity
    • Vulnerable to vaginal infections
  — Vaginal dryness leading to vaginal atrophy
Effect of Estrogen Depletion on the Urinary Tract

• Estrogen depletion causes the lining of urethra to become drier, thinner and less elastic; coupled with the more alkaline environment in the vagina this can lead to:
  – Increased risk of UTIs
  – Incontinence
The Ideal SERM

• Decrease hot flushes

• Increase bone density

• Prevent fractures in spine and hip

• Prevent breast cancer

• Improve cardiovascular health

• Lubricate the vagina

• No effect on the endometrium

Vaginal Atrophy Pathophysiology: Cellular Changes

- **Superficial**
- **Intermediate**
- **Parabasal**

**Thick, healthy, well-estrogenized lining of the vagina in premenopausal women**

- Intermediate and superficial cells predominate in premenopausal women; minimal parabasal cells.

**Thin, dry lining of vagina due to menopause (after estrogen loss)**

- After menopause, there is an increase in parabasal and intermediate cells and a substantial decrease in superficial cells.


**EFFICACY PROFILE - VAGINA**
Visualizing Vaginal Atrophy

Premenopause

Vaginal cells are large, flat, with small nuclei

Postmenopause

Cells thin, dry, clumped together with large nuclei; may cause soreness, increased likelihood of infection
DT56a & Vaginal Atrophy Clinical Study

- 12 post-menopausal women with severe vaginal atrophy
  - 100% parabasal cells on cervical cytology
    - Dyspareunia- 5, Vaginal soreness- 3, Vaginal dryness- 2, Vaginal irritation-1, Bleeding with coitus-1

- 12 week open-label study & follow up after 2 yrs.

- Assessment of:
  - Vaginal atrophy - speculum exam, maturation index, vaginal pH, pap smears
  - Utian Quality of Life Questionnaire (UQoL)
  - blood work

Reduction of Vaginal pH Following 12 weeks of DT56a Treatment

- Vaginal pH decreased in all women

Maturation Index Pre & Post Treatment- 12 weeks

- All patients reported significant improvement in their most bothersome symptom

Maturation Index after 2 Years on DT56a

- Improvement in maturation index increased with prolonged use
### Utian Quality of Life (QoL) Questionnaire

<table>
<thead>
<tr>
<th>Item</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am able to control things in my life that are important to me</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>2. I feel challenged by my work</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>3. I believe my work benefits society</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>4. I am not content with my sexual life</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>5. I am content with my romantic life</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>6. I have gotten a lot of personal recognition in my community or at my job</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>7. I am unhappy with my appearance</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>8. My diet is not nutritionally sound</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>9. I feel in control of my eating behavior</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>10. Routinely, I engage in active exercise three or more times a week</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>11. My mood is generally depressed</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>12. I frequently experience anxiety</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>13. Most things that happen to me are out of my control</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>14. I am content with the frequency of my sexual interactions with a partner</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>15. I currently experience physical discomfort or pain during sexual activity</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>16. I believe I have no control over my physical health</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>17. I am proud of my occupational accomplishments</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>18. I consider my life stimulating</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>19. I continue to set new personal goals for myself</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>20. I expect that good things will happen in my life</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>21. I feel physically well</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>22. I feel physically fit</td>
<td>1.00</td>
<td>5.00</td>
</tr>
<tr>
<td>23. I continue to set new professional goals for myself</td>
<td>1.00</td>
<td>5.00</td>
</tr>
</tbody>
</table>

Utian scale domain

- Occupational: 10.00 - 35.00
- Health-related: 10.00 - 35.00
- Emotional: 9.00 - 30.00
- Sexual: 3.00 - 15.00
- Total: 40.00 - 110.00

Minimum, 1 (not true of me); maximum, 5 (very true of me).
Improvement in Utian Sexual QOL questionnaire following 12 weeks of treatment with DT56a

Mean pre-treatment 6.5 ± 2
Mean post-treatment 10.6 ± 3.2
p< 0.001 (Paired T test)

- Stat. significant improvement in sexual QOL part of the questionnaire

Soy Alternatives Reduced Parabasal Cells and Increased Percent of Superficial Cells

The increase in superficial cells was significantly different between treatments * (P=0.035): (6 ± 11 vs. 4 ± 14%) at 8 weeks.

Effect of Estrogen Depletion in the Bone

• The estrogen depletion that comes with menopause results in:
  – Acceleration of osteoclast activity while osteoblast activity is motivated by estrogenic response ceases
  – Enhanced bone loss, developing into osteopenia and the development of osteoporosis
Menopause Is Associated With an Accelerated Loss of Bone Mass

The Ideal SERM

• Decrease hot flushes

• **Increase bone density**
  • Prevent fractures in spine and hip
  • Prevent breast cancer
  • Improve cardiovascular health
  • Lubricate the vagina

• No effect on the endometrium
Effect of DT56ae on BMD Clinical Study

• 98 healthy postmenopausal women (55 ± 5)
  – Study Group: 644 mg/d DT56a (n=39)
  – Low Dose Group: 344 mg/d DT56a + calcium (n=43)

• BMD test as was done through DEXA scan at time 0 and after 12 months of treatment.

• Vaginal ultrasound and blood tests were done at time 0 and after 12 months.

Effect of DT56a on BMD Clinical Study

- BMD test was done through DEXA scan at time 0 and after 12 months of treatment.
  - 98 postmenopausal women (55 ± 5)

- 3.6% increase in spine
- 2.0% increase in hip

Effect of DT56a on BMD Clinical Study

• No change in vaginal ultrasound
• No change of sex hormone levels
  – FSH & E₂ levels - unchanged
• No reported side effects

• DT56a was seen to significantly detain bone loss, thus, providing a good bone health management therapy
Mechanism of Action in Skeletal Tissue
Osteoblasts Activation

• DT56a *promotes Osteoblast activity*, reversing the bone loss process through new bone formation

• DT56a is a unique agent for detaining postmenopausal bone loss and the development of Osteoporosis

Mechanism of Action of DT56a as a SERM

**Results:**

- Femarelle stimulates Creatine Kinase (CK) activity, a marker of ER activity (agonist), in the epiphyseal cartilage and diaphyseal bone.
- Contrary to the estrogen group, there was no estrogenic effect on the uterus with Femarelle.

Somjen D, Yoles I. “DT56a (Tofupill/Femarelle), selectively stimulates creatine kinase specific activity in skeletal tissues of rats but not in the uterus” *J. of Steroid Biochemistry & Molecular Biology* 2003;86(1):93-98
Effect of Raloxifene on fracture rates

- Clinical fractures: All subjects, N = 7705
- Vertebral fractures: No baseline fractures, N = 3604
- Vertebral fractures: Baseline fractures, N = 2641

Comparison of fracture rates across different treatment groups:
- Placebo
- 60mg
- 120mg
Kaplan-Meier fracture rate (%)

- **Placebo**
  - Vertebral fractures: 4.1%
  - Nonvertebral fractures: 6.3%
- Bazedoxifene 20 mg
  - Vertebral fractures: 2.3%
  - Nonvertebral fractures: 5.7%
- Bazedoxifene 40 mg
  - Vertebral fractures: 2.5%
  - Nonvertebral fractures: 5.6%
- Bazedoxifene 60 mg
  - Vertebral fractures: 2.3%
  - Nonvertebral fractures: 5.9%
- Raloxifene 60 mg
  - Vertebral fractures: 2.3%
  - Nonvertebral fractures: 5.9%

**Results:**

- **RRR, 42%; HR, 0.58 (95% CI, 0.38–0.89)**
- **RRR, 37%; HR, 0.63 (95% CI, 0.42–0.96)**
- **RRR, 42%; HR, 0.58 (95% CI, 0.38–0.89)**

**Notes:**

- **n.s.** indicates a non-significant result.
The Ideal SERM

• Decrease hot flushes
• Increase bone density
• Prevent fractures in spine and hip
• Prevent breast cancer

• **No adverse effect of clotting**
  • Improve cardiovascular health
  • Lubricate the vagina
  • No effect on the endometrium

Effect of DT56a on Clotting Clinical Study

• In two different clinical trials, 116 symptomatic menopausal women were screened for their clotting times through a Platelet Function Analyzer (PFA-100 Siemens)
  – The instrument measures the closure time (CT) in sec. it takes for platelets in whole blood to block the flow through a perforated membrane coated with:
    • Collagen and Epinephrine (CEPI)
    • Collagen and Adenosine Diphosphate (CADP)
  – CT is a combined measure of platelet adhesion, aggregation, and the blood coagulation factors

• Nachtigall L et al. The Selective Estrogen Receptor Modulator (SERM) DT56a (Femarelle), does not affect platelet reactivity in normal or thrombophilic menopausal women. *Menopause* 2011;18(3):285-288
Effect of DT56a on Clotting
Clinical Study

<table>
<thead>
<tr>
<th>Method</th>
<th>CADP (sec)</th>
<th>CEPI (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>71-118</td>
<td>85-165</td>
</tr>
<tr>
<td>Borderline</td>
<td>56-70</td>
<td>70-84</td>
</tr>
<tr>
<td>Pathological</td>
<td>&lt;56</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>
Oral vs. Transdermal Estrogen in Women with Increased Clotting Risk (“Borderline”)

- 13 women with borderline CT
  - Oral ET - 5 women
  - Trans. ET - 8 women
- Clotting time of borderline women on oral ET decreased CT to pathological levels

<table>
<thead>
<tr>
<th></th>
<th>CADP (sec)</th>
<th>CEPI (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>71-118</td>
<td>85-165</td>
</tr>
<tr>
<td>Borderline</td>
<td>56-70</td>
<td>70-84</td>
</tr>
<tr>
<td>Pathological</td>
<td>&lt;56</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

Average Clotting Time of 25 “Normal” Women on Femarelle

No change in platelet adherence-time in women with normal clotting time
Thrombophilic women & DT56a Clinical Study

Genetic Diagnosis of 7 Women with Short CT (Thrombophilic Women)

| n=4          | Factor V Leiden        |
| n=1          | Mutant Prothrombin     |
| n=1          | Protein S Deficiency   |
| n=1          | Elevated Anticardiolipins Antibodies |

CT of 7 Thrombophilic Women on Femarelle® Over 1 Year

- Closure times were measured following:
  - 3 weeks
  - 8 weeks
  - 12 months

- Femarelle did not affect clotting parameters in either normal clotting group (25) nor in the thrombophilic women

Nachtigall L et al. The Selective Estrogen Receptor Modulator (SERM) DT56a (Femarelle), does not affect platelet reactivity in normal or thrombophilic menopausal women. *Menopause* 2011;18(3):285-288
Use of Alternative Supplements to Treat Menopausal Symptoms

- 30 - 40% adults surveyed have used an alternative treatment
- In the US $27 billion spent annually on alternative therapies
- Commonly used treatments include dong quai, black cohosh, ginseng and Lignans

## Three Major Classes of Phytoestrogens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Therapeutic Claims</th>
<th>Pharmacology</th>
<th>Side Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dong Quai (Angelica Sinensis)</td>
<td>- Used in premenstrual syndrome formulas as well as menopausal formulas.</td>
<td>- Active ingredients may be phytoestrogens.</td>
<td>- None reported</td>
</tr>
<tr>
<td>Black Cohosh (Cimicifuga racemosa)</td>
<td>- Relief of menopausal symptoms. Approved in Germany to treat perimenopausal symptoms.</td>
<td>- Active compounds may include actein and isoferulic acid</td>
<td>- Common adverse effects include gastric discomfort.</td>
</tr>
<tr>
<td>Soy Beans (Glycine max)</td>
<td>- 25 g/day Soy protein reduces cholesterol levels.</td>
<td>- Flavonoids and isoflavonoids (D, G and Glycitein) predominantly as glycosides</td>
<td>- Very high doses may cause vomiting, headaches, dizziness, lowered blood pressure, and limb pain.</td>
</tr>
<tr>
<td></td>
<td>- Relief of menopausal symptoms.</td>
<td>- Also contains saponins and phytosterols which may be active agents</td>
<td></td>
</tr>
</tbody>
</table>

**GRAS**= Generally recognized as safe.
Phytoestrogens for Complications of Menopause

- Hot flashes/sweating
- Osteoporosis, BMD
- Vaginal atrophy
- Cardiovascular
- Skin
- Cognitive function, mood
- Platelet aggregation
The ideal SERM should also benefit other symptoms related to climacteric syndrome.
Lipid Parameters Improved with 40 mg/day Legnans

Design
- Randomized, double-blind, placebo-controlled, 12 weeks
- (N=100)
- Placebo + 40 mg Legnans

Jeri A. 10th World Congress Menopause, 2002, Berlin, Germany.
Effect of Estrogen Depletion on the Skin

• The reduction of estrogen at menopause decreases the water-holding ability and elasticity in the skin, leading to:
  – Increase in wrinkling and sagging
  – Dryness
  – Skin bruising easily
Beneficial Effects of Soy Alternatives on Skin

Histological gluteal skin section from a patient before and after treatment with soy alternative

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial thickness (μm)</td>
<td>560.8</td>
<td>613.0</td>
</tr>
<tr>
<td>Epidermal papillar index (%)</td>
<td>10.4</td>
<td>14.7</td>
</tr>
<tr>
<td>Dermal collagen (no units)</td>
<td>152.0</td>
<td>163.0</td>
</tr>
<tr>
<td>Elastic fibers (no units)</td>
<td>525.4</td>
<td>611.2</td>
</tr>
<tr>
<td>Dermal vessels (number per slide)</td>
<td>64.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

(N=30) 100 mg/day soy extract for 6 months.

These results suggest that isoflavone supplementation has a favorable effect on cognitive function, particularly verbal memory, in postmenopausal women.

The Ideal SERM

• Decrease hot flushes

• Increase bone density

• Prevent fractures in spine and hip

• **Prevent breast cancer**

• Improve cardiovascular health

• Lubricate the vagina

• No effect on the endometrium
Effect of DT56a on ER+ Breast Cancer Tissue Culture

DT56a did not trigger cancer cell growth, showing its antagonistic activity on the breast.

What do we know about Relizen’s impact on breast cancer cells?

No Stimulation of Breast Cancer Cells

- An E-Screen in vitro test was performed using MCF-7 cells, an immortalized human breast carcinoma cell line that endogenously expresses estrogen receptors.
- In comparison to 17-beta estradiol, Relizen did not stimulate the proliferation of MCF-7 breast tumor cells.

Relizen does not stimulate proliferation of MCF-7 breast cancer cells.

Soy isoflavones consumption and risk of breast cancer incidence or recurrence: meta-analysis

Statistically significant reduction of 11%

Lignans consumption and risk of breast cancer incidence or recurrence: meta-analysis

Statistically significant reduction of 16%

Summary

• Numerous studies have investigated both the efficacy and the safety of SERMS
• Allows for evidenced-based recommendations for menopausal women
  – Decreases hot flashes
  – Increases bone density
  – No increased proliferation or density in the breast
  – No increased proliferation in the endometrium
  – No increase in clotting
  – May be used in high risk women ie Diabetes, Obesity
• SERMs and lifestyle modification are associated with improvement in signs and symptoms of the climacteric syndrome as well as c/v disease, mood and appearance
• SERMs can advance the management of the menopause