New Pharmacology Compounds for Female Sexual Dysfunction: Peripheral Agents

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Pharmacology:
branch of medicine and biology concerned with study of drug action where a drug can be broadly defined as any man-made, natural, or endogenous (within the cell) molecule which exerts a biochemical and/or physiological effect on the cell, tissue, organ, or organism
Sexual Pharmacology – Peripheral Agents

**Peripherally – Acting Hormones**
- Vestibular and Vaginal Estradiol
- Vestibular and Vaginal Estradiol and Testosterone
- Intravaginal DHEA

**Peripherally – Acting Non-Hormones**
- Vasodilator
- Vasoconstrictor
- Skeletal Muscle Relaxants
- Pain Management
- Other
MENOPAUSE MANAGEMENT – FIVE TREATMENTS

**Testosterone Therapy**
- Use FDA-approved testosterone at 10% of male dose
  1. Daily transdermal gel - 1/10th tube daily to calf/thigh
  2. Weekly IM injections - 0.1 ml - 50 mg/ml testosterone enanthate/cypionate - into vastus lateralis muscle – anterolateral mid-thigh; 27 gauge needle; 1 ml syringe
  3. 4-6 month subcutaneous testosterone pellet

**Estradiol Therapy**
- Consider FDA-approved biologically identical estradiol
  1. Daily oral (↑SHBG, ↑VTE, ↑lipids)
  2. Daily transdermal gel, emulsion, spray
  3. Twice weekly, weekly transdermal patch
  4. Three month vaginal ring
  5. Weekly IM injections - 0.1 ml – estradiol valerate 10 mg/ml; 5 ml bottle; vastus lateralis muscle – anterolateral mid-thigh - 27 gauge needle; 1 ml syringe

**Progesterone Therapy**
- Consider FDA-approved biologically identical progesterone
  1. Oral micronized progesterone 100 mg q MWF (intact uterus, q MTh hysterectomy)
  2. Vaginal progesterone suppository – 6 per month
  3. Compound progesterone cream

**Vestibular Hormonal Therapy**
- Compound estradiol 0.02%/testosterone 0.1% in hypoallergenic base (methylcellulose); apply pea-sized volume x 2 (right and left sides; directly onto entire vestibule; QD – BID

**Intravaginal Hormonal Therapy**
- Daily compound estradiol 0.02%/testosterone 0.1% in hypoallergenic base (methylcellulose); apply pea-sized volume directly into vagina
- Daily vaginal estradiol cream – pea-sized amount
- Daily 10 mg DHEA tablet/1% DHEA suppository
- Three month vaginal ring

Members of the consensus conference agreed that the term genitourinary syndrome of menopause (GSM) is a medically more accurate, all-encompassing, and publicly acceptable term than vulvovaginal atrophy.
Vulvo-Vaginal Atrophy - Genito-Urinary Syndrome of Menopause

- 45% post-menopausal & currently or previously experienced Vulvo-Vaginal Atrophy VVA/GSM sx
- 4% attributed sx to GSM/VVA;
- 63% failed to recognize GSM/VVA as chronic
- 75% stated vaginal atrophy had negative impact
- Trend away from oral, - toward topical hormones
- Safety concerns, lack of MD recommendation major reasons for discontinuing or not using

Nappi RE, Kokot-Kierepa M. Climacteric 2012; Early Online 1-9.
Two Estradiol-Dependent Organs – During Vulvoscopy

Labia minora
Vagina

Low Estrogen State

Robust Estrogen State

Resorption of Labia Minora

Labia Minora Normally Meet at Posterior Fourchette

Reduced vaginal rugae, pH >5

Robust vaginal rugae, pH 4

Local Vaginal Estrogen

- Much lower doses of estrogen applied vaginally are effective with minimal elevation of serum estradiol levels.
- In one study, use of local vaginal cream was associated with better symptom relief than oral dose, even with lower systemic levels seen.

Vaginal estrogen receptors are dependent in part on estradiol – inverse relationship compared to the uterus.
Differential Effects of Estradiol, Progesterone, and Testosterone on Vaginal Structural Integrity

Monica A. Pessina, Richard F. Hoyt, Jr., Irwin Goldstein, and Abdulmaged M. Traish
Endocrinology 147(1):61-69, 2005
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Epithelium: Effects of Various Doses of Estradiol on ER-a

Slides immunostained for ER-alpha using ABC method with DAB.
Slides photographed at 400X

* P<0.01 vs Control
† p<0.01 versus Ox

Effects of estradiol on the proportion of ER-α immunoreactive cells in the epithelium
# Sexual Pharmacology – Peripheral Agents

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VULVODYNIA – ANATOMY OF VULVA, VESTIBULE, VAGINA

Embryology:
Mesoderm (vagina)
Endoderm (vestibule)
Ectoderm (vulva)
Hormonally Mediated Provoked Vestibulodynia

Negative Internal Controls for AR

Positive staining AR
Negative staining- AR

Vestibular glands – Control Group

Without Provoked Vestibulodynia

Positive cellular nuclei staining with anti-androgen receptor (AR)

With Provoked Vestibulodynia

Positive External Controls for AR

Hematoxylin-eosin staining: To evaluate inflammation and squamous metaplasia within glandular structures

Vestibular glands – Control
Vestibular gland – Provoked Vestibulodynia

HISTOLOGY
Hematoxylin-eosin staining: To evaluate inflammation VVS and squamous metaplasia within glandular structures

Chronic inflammatory infiltrate
Replacement of columnar epithelium by squamous metaplasia

Vestibular glands – Control
Vestibular glands – Provoked Vestibulodynia

Prostate sections
Vestibulodynia
The pain is confined to the vestibule: it (generally) stops outside of Hart’s line and there is (generally) no pain inside the vagina.

- The pain is throughout the entire vestibule. (If the pain is significantly worse in the back part of the vestibule consider a dual diagnosis, and follow the next decision tree the right as well)
- The pain is much worse at 4, 6, & 8 o’clock position of the vestibule (and there is minimal or no pain on either side of the urethra.)
  - There may be tenderness when deep pressure is applied to the perineum
- The pain is mainly in the vestibule but there is irritation, redness, and (possibly fissures) on the prepuce or in the grooves between the labia minora and majora.
- Ulcers or erosions that may be confined to the vestibule but may also occur on the labia and perineum.

Hormonally mediated vestibulodynia
- The pain began
  - While taking hormonal contraceptives or other medications that affect reproductive hormones, such as those for endometriosis, breast cancer, acne, infertility or removal of ovaries.
  - While breastfeeding, perimenopause or postmenopause, or during abnormal or missing menstrual cycles.
  - Pain is also associated with low calculated free testosterone levels; decreased libido, arousal or energy; or depression

Congenital neuroproliferative vestibulodynia
- Pain since first tampon insertion or first attempt at intercourse
- Never completely pain-free
- Sensitivity or pain when pushing in on the belly button but none when pressure on the rest of the abdomen. The pain may radiate towards the vagina.

Acquired neuroproliferative vestibulodynia
- The pain began after:
  - A severe allergic reaction to a topical medication
  - A severe yeast infection
- More likely in women with a history of very sensitive skin or irritant or allergic reactions.
- Women may have certain genetic polymorphisms.

Hypertonic pelvic floor dysfunction
- The muscles of the pelvic floor are tight and tender when examined by an experienced doctor or physical therapist; also an abnormal EMG of the pelvic floor muscles

Vaginitis
- Inflammation that includes the vestibule and vaginal mucosa. The vaginal mucosa typically looks inflamed and there is frequently yellowish discharge.
  - Bacterial vaginosis does not cause enough inflammation to cause vestibulodynia

Desquamative inflammation vaginitis (DIV)
- Thick, yellowish discharge that dries like glue and ruins underwear. The vaginal pH is >5.0 with numerous white blood cells and parakelial cells on wet mount

Allergic vaginitis
- Semen allergy: swollen and inflamed vagina and vestibule that only occurs when condom is not used during intercourse
  - Latex or spermicide allergy: swollen and inflamed vagina and vestibule that only occurs when condoms are not used during intercourse

Lichen planus
- Ulceration in the vestibule that can have “fern-like” or violet borders. The erosions can extend into the vagina and can also affect the mouth. Very significant scarring of the vulva and vagina possible.

Lichen Sclerosus
- Ulcerations in the vestibule and labia but not in the vagina. Thick, white, itchy skin with very significant scarring.

Candidiasis
- Positive culture for yeast infections that do not respond to three doses of fluconazole.
Most commonly caused by hormonal contraceptives (may not resolve just by stopping OCPs.)
Other causes include: menopause, oophorectomy, hormonal control of endometriosis or hirsutism, breast-feeding, infertility treatments, treatment of breast cancer

Hormonally Mediated Provoked Vestibulodynia

Diffuse vestibular tenderness of the entire vestibule

Ostia of glands are frequently erythematous

The vestibule may have a diffuse pallor with superimposed erythema

Low estradiol, low free testosterone, very high SHBG

Hormonally Mediated Provoked Vestibulodynia

Treatment:
Stop hormonal contraceptives
Systemic testosterone – ideal calculated free testosterone 0.8 ng/dl
Local to vestibule estradiol 0.02%/testosterone 0.1% in methylcellulose BID
Expect no improvement for 6 weeks, 30-40% by 12 weeks

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216 post-menopausal women with vaginal atrophy (ITT Population)

0.0% (Placebo; n=53)
0.25% (3.25 mg DHEA; n=53)
0.5% (6.5 mg DHEA; n=56)
1.0% (13 mg DHEA; n=54)

Daily intravaginal application of one ovule for 12 weeks
PARABASAL CELLS

Labrie et al., Menopause 16, 907-922, 2009
0.5% DHEA vs baseline
p=0.83

vs placebo
p<0.0001

% parabasal cells

% superficial cells

pH

Pain at sexual activity

Labrie et al., Menopause 16, 907-922, 2009
ENDOMETRIUM

The enzymes required to transform DHEA into estrogens are absent in the endometrium.
DHEA

Vaginal changes

Desire – Arousal – Orgasm – Pleasure
MENQOL: Sexual Domain

![Graph showing the effect of DHEA dose on sexual domain score](image)

- **vs Baseline**
  - 0%: p=0.0002
  - 0.25%: p=0.0001
  - 0.5%: p=0.0036
  - 1.0%: p<0.0001

- **vs Placebo**
  - Baseline
  - 12 weeks
Abbreviated Sexual Function - Desire Domain

Labrie et al., Menopause 16, 923-931, 2009
DHEA action on the rat vaginal wall

Analogy with the human skin where DHEA has been found to stimulate collagen formation and decrease skin wrinkles*

Calvo et al., JSBMB 112, 186-193, 2008
Labrie et al., Unpublished data

Berger et al., JSBMB 96, 201-215, 2005
Immunohistochemical staining of the fibers in the rat vagina

E: Epithelium
LP: Lamina Propria (or Stroma)
M: Muscle
→: Stained TH fibers
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Metabolic Syndrome
Arterial occlusive pathology in the ilio-hypogastric-pudendal arterial bed

downward arrows:
- vaginal lubrication
- vaginal wall pressures
- vaginal length/width
- clitoral blood flow

Pelvic genitalia


Tadalafil 5 mg Daily Treatment for Type 1 Diabetic Premenopausal Women Affected by Sexual Genital Arousal Disorder

Salvatore Caruso, MD, Carla Cicero, MD, Mattea Romano, MD, Lucia Lo Presti, MD, Betty Ventura, MD, and Chiara Malandrino, MD
Research Group for Sexology—Department of Medical and Surgical Specialties, University of Catania, Azienda Ospedaliero—Universitaria Policlinico di Catania, Catania, Italy

Table 1 Changes in Short Personal Experience Questionnaire (SPEQ) scores from baseline to 12th week daily tadalafil 5 mg intake

<table>
<thead>
<tr>
<th>Sexual activity by SPEQ</th>
<th>Baseline (N = 33)</th>
<th>12 weeks (N = 32)</th>
<th>P</th>
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<tbody>
<tr>
<td>Desire</td>
<td>4.0 ± 1.3</td>
<td>3.7 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Arousal</td>
<td>2.5 ± 1.2</td>
<td>4.2 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Orgasm</td>
<td>2.7 ± 1.4</td>
<td>3.9 ± 0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Enjoyment</td>
<td>3.4 ± 1.1</td>
<td>4.0 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Satisfied by frequency</td>
<td>3.0 ± 1.1</td>
<td>4.0 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of intercourse</td>
<td>2.8 ± 1.0</td>
<td>3.0 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Frequency of fantasies</td>
<td>2.1 ± 0.7</td>
<td>3.1 ± 0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total score</td>
<td>20.9 ± 1.1</td>
<td>26.2 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>2.3 ± 1.1</td>
<td>1.1 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
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Note: Values are means ± standard deviation
P value determined by nonparametric Wilcoxon’s rank-sum test
NS = not significant

Figure 1 Short Form-36 (SF-36) Quality of Life scores in diabetic type 1 women on tadalafil 5 mg intake, compared with baseline values. *P < 0.05.
Based on limited current data, there appears to be an association between female sexual health and vascular risk factors (hypertension, hyperlipidemia, metabolic syndrome/obesity, diabetes, and coronary heart disease). More research is needed.