Cancer and Sexuality in Women
Treatment Considerations

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Disclosures

• No disclosures
Case 1

• 40 yr. old with ER+/PR+ right breast cancer. She was having regular menses prior to diagnosis.

• She was treated with lumpectomy, adjuvant chemotherapy with AC/Paclitaxel, followed by radiation. Her cycles stopped after her first round of chemo. She had awful hot flashes disrupting her sleep but started to feel better by the end of radiation.

• She then started hormonal therapy with ovarian suppression and letrozole. Her hot flashes and sleep difficulties returned, and now has severe vaginal dryness, sexual pain and low libido and she comes to you for treatment.
Sexuality and Cancer

Priorities are not the same for all women

- Sexual response
  - Desire
  - Arousal
  - Orgasm

- Fertility
  - Hope for motherhood

- Sexual Identity
  - Changes in Anatomy
  - Being Female

- Body image
  - Feeling attractive
  - Pride

- Self esteem, Sense in life, Commitment
Key Concepts on Cancer and Women’s Health

• Menopausal vasomotor symptoms are often more severe in cancer survivors

• Surgical treatments may include oophorectomy with immediate onset of surgical menopause
• Premenopausal women with normal menstrual functioning may have ovarian shutdown with chemotherapy
• Postmenopausal women taking menopausal hormone therapy (MHT) tend to abruptly stop when diagnosed with breast or gyn cancer
• Vasomotor symptoms common with hormonal drugs like tamoxifen or aromatase inhibitors
• New data confirming that ovarian suppression with AI is better than SERM in premenopausal women
  • HOBOE-2 (Hormonal BOne Effects-2) phase 3 trial
Can Ovarian Toxicity be Prevented?

- POEMS (Prevention of Early Menopause) prospective international, phase 3, randomized trial to see whether GnRH agonist with chemotherapy would reduce the rate of ovarian failure after adjuvant or neoadjuvant treatment of hormone-receptor–negative early breast cancer

- 2004-2011, 4 year follow up

- 218 women with stage I-III hormone-negative breast cancer given goserelin (GnRH agonist) with chemotherapy vs. chemotherapy alone

- OR 2.34 (23% pregnant vs 12% in gosrelin vs no gosrelin arm)

Moere et al JNCI 2018
Can Ovarian Toxicity be Prevented?

• Results: **More pregnancies and more live births with goserelin**

  • Ovarian failure: 22% in chemo arm vs 8% in goserelin arm 
    \( (P = .04) \)

  • Pregnancy: 12% in chemo arm vs. 23.1% in goserelin arm 
    \( (P < 0.05) \)

  • Live Births: 12 in chemo arm (7%) vs. 18 in the goserelin arm 
    \( (15\%, 18, P = .05) \)

  • 5-year DFS: 78% in chemo arm and 88% in goserelin arm 
    \( (P = .04) \)

  • 4-year OS: 82% in chemo arm vs 92% in goserelin arm \( (P = .06) \)
Treatment Options for Menopausal Hot Flashes In Female Survivors

- Over-the-counter (OTC) options
- Prescription alternatives
- Integrative therapies
- Hormonal therapies
  - Combination of estrogen + progesterone if intact uterus, estrogen alone if prior hysterectomy
  - Novel therapies that combine a selective estrogen receptor modulator (SERM) with estrogen creating a tissue selective estrogen complex (TSEC)
- Lifestyle interventions – weight loss if obese
Non-Hormonal Pharmacologic Treatments for Hot Flashes

• Antidepressants: Venlafaxine (best studied) paroxetine, fluoxetine, citalopram, escitalopram, desvenlafaxine, mirtazapine, sertraline

• Gabapentin and Pregabalin

• Much of data showing a benefit in short trials less than 12 weeks

• Beneficial effects in days and doses typically lower than that for depression- most effective dose of venlafaxine 75 mg per day in divided doses

• Side Effects: dry mouth, decreased appetite, fatigue, nausea, constipation and sexual disturbances
Clinical Pearls for Non-Hormonal Pharmacologic Treatments

• Start with lowest dose possible!

• Best studied, venlafaxine: start with low doses to avoid discontinuation – lowest is 25 mg but scored, most effective dose 75 mg typically in divided doses

• For pure SSRI’s start with 10 mg

• If using gabapentin – 900 mg most well studied, use at night as SEDATION is common side effect. Start with 100-300 mg and increase up to a max of 2400 mg in divided doses
How To Manage All the Vaginal Dryness – OTC Options

• Vaginal moisturizers – retain water and provide longer term relief
• Oils- penetrate thin tissue and soothing
• Topical vitamins- D or E, liquid or suppositories
• pH-balanced gels with hyaluronic acid
• Soothing agents for vaginal or vulvar pain
• Topical anesthetics for introital discomfort
• Lubricants for sexual activity
  • Most of these products get to market typically with little data- only takes 12 week trials to show effectiveness and safety
  • Many do NOT have safe and healthy pH and osmolality
Vaginal Dryness: Local vs. Systemic Estrogen

- Local estrogen therapy is generally preferred for vaginal dryness/dyspareunia
  - Targeted efficacy to vaginal tissues
  - Minimal systemic absorption, fewer adverse effects
  - Progestin component is not needed in women with uterus

- Local estrogen thought to improve lubrication, increase blood flow and sensation in vaginal tissues
Topical Steroids

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition (Product Name)</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| **Cream**   | **17β estradiol** (Estrace®)  
**Conjugated estrogens** (Premarin®) | **Initial:** 2-4 g/d for 1-2 wk  
**Maintenance:** 1 g/3xweek (0.1 mg active ingredient/g)  
0.5-2 g/3xwk (0.625 mg active ingredient/g) |
| Tablet      | Estradiol hemihydrate (Vagifem®)(Yuvaferm) (Imvexxy®) | **Initial:** 10 mcg/d for 2 wk *4mcg  
**Maintenance:** 10 mcg twice/wk |
| Ring        | **17β estradiol** (Estring®) | **Device contains 2 mg**  
**Releases 7.5 mcg/d for 90 d** |

- For patients with a hormone sensitive breast cancer, favor tablets or ring
- Can also use prasterone, FDA approved, strong data showing no elevation in systemic hormones
- Can consider topical T(0.01-0.1%), again know your compounding pharmacy
What if she has a HR+ Breast Cancer??

Consensus Recommendations

Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women’s Sexual Health

Stephanie S. Faubion, MD, FACP, NCMP, IF,1 Lisa C. Larkin, MD, FACP, NCMP, IF,2 Cynthia A. Stuenkel, MD, NCMP,3 Gloria A. Bachmann, MD,4 Lisa A. Chism, DNP, APRN, BC, NCMP, CSC, FAANP,5 Risa Kagan, MD, FACOG, CCD, NCMP,6 Andrew M. Kaunitz, MD, FACOG, NCMP,7 Michael L. Krychman, MD, FACOG, MPH, IF,8 Sharon J. Parish, MD, IF, NCMP,9 Ann H. Partridge, MD, MPH,10 JoAnn V. Pinkerton, MD, FACOG, NCMP,11 Tami S. Rowen, MD, MS,12 Marla Shapiro, CM, MDCM, CCFP, MHSC, FRCPC, FCFP, NCMP,13 James A. Simon, MD, CCD, NCMP, IF, FACOG,14 Shari B. Goldfarb, MD,15 and Sheryl A. Kingsberg, PhD16
Details on Guidelines

• Evidence Based and Expert opinion
• There is no study looking at the main clinical outcome of concern: breast cancer recurrence
  • Recurrence HAS been shown in survivors who used systemic HT
• At most we have surrogate marker in terms of systemic hormone changes in response to local application
Who are good candidates for local therapy?

Key takeaways: one size does not fit all
Many oncologists are comfortable with local estrogen therapy in HR pos patients even if on AIs
Important Considerations of Local Hormones

• Absorption of local ET varies by the active ingredient
  • potency: conjugated equine estrogens (CEE)>estradiol>estrone>estriol

• Creams absorbed to higher surface area than ring/tablets

• Vulva less vascular/less absorption compared to the vagina, esp upper third

• Consider most sx are on vulva/entrance to vagina, keep cream there

• Consider vaginal DHEA(prasterone)
  • Need more data in women on AIs

• Do not recommend ospemifene in HR pos breast cancer
Vaginal Dryness and Sexual Functioning

• Important to treat the vaginal dryness first and libido after!
• If hurts to be touched or have penetration, desire for sex will be affected
• Once their pain is addressed, can then discuss HSDD, FSAD FOD
  • Can use nearly all options reviewed in this course
  • Exception is systemic T for HR+breast cancer!
  • Flibanserin not approved for postmenopausal women
    • However evidence shows efficacy!
What About Low Desire???
What is the data for off label antidepressants?

Bupropion

- Norepinephrine-dopamine reuptake inhibitor (NDRI)
  - Inhibits dopamine transporter and norepinephrine transporter
- Investigated in several clinical trials for the treatment of HSDD
  - Bupropion improved sexual function (as measured by CSFQ and BISF-W), but had no effect on frequency
  - Evidence to show adjunctive treatment helps treat SSRI induced FSD, including desire

BISF-W, Brief Index of Sexual Functioning in Women; CSFQ - Changes in Sexual Functioning Questionnaire
FSFI: Female Sexual Function Index

Safarinejad MR.. J Psychopharmacol. 2011
What about other antidepressants

Buspirone

• Presynaptic serotonin 5-HT$_{1A}$ partial agonist
  – Greater presynaptic than postsynaptic effects, resulting in a reduction in serotonergic tone

• Post hoc analysis of add-on buspirone to selective serotonin reuptake inhibitors (SSRI) for the treatment of depression
  – 58% of subjects treated with buspirone reported an improvement in sexual function, compared with 30% treated with placebo

  – There are no studies looking at buspirone where primary outcome is FSD

Loane C, Politis M. *Brain Res.* 2012;1461:111-118.
What About Flibanserin?

• Mixed post-synaptic 5HT1A agonist and 5HT2A antagonist
  – 5HT1A agonists could have pro-sexual effects.
  – Stimulating 5HT2A receptor has been associated with decreased sexual behavior (male rodents)
• Also activates dopamine D4 receptors
• Moderate affinity for 5HT2B and 5HT2C receptors

• Flibanserin is thought to produce region-specific elevations in dopamine and norepinephrine, and may help to offset inhibitory serotonergic activity impacting desire pathways
  • *Phase 1 studies started in 1995 for depression, HSDD studies started in 2002*
Flibanserin Pivotal Studies

Study 147

Monthly Frequency, Mean ± SE

Placebo  Flibanserin 100 mg qhs

SSEs

Study 71

Monthly Frequency, Mean ± SE

Placebo  Flibanserin 100 mg qhs

FSFI-Desire

Study 75

Monthly Frequency, Mean ± SE

Placebo  Flibanserin 100 mg qhs

FSDS-R13 (Distress)

* p < 0.05; ** p < 0.01
LS=least squares.

But What About the Side Effects?

<table>
<thead>
<tr>
<th></th>
<th>Flibanserin</th>
<th>Bupropion</th>
<th>Buspirone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>11.4%</td>
<td>Tremor</td>
<td>13.5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11.2%</td>
<td>Agitation</td>
<td>9.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.4%</td>
<td>Dry Mouth</td>
<td>9.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.2%</td>
<td>Constipation</td>
<td>8.7%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.9%</td>
<td>Excessive sweating</td>
<td>7.7%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2.4%</td>
<td>Dizziness</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Kingsberg et al Sex Med Rev 2019
**What’s the Concern about Alcohol?**

**Phase 1 Alcohol Challenge Study**

Study consisted of 5 single dose study periods; subjects received each of the 5 treatments.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Dosing Regimen</th>
<th>0.4 g/kg EtOH is equivalent to each of the following in a 70 kg (~154 lb) person:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 25 subjects</td>
<td>A. 0.8 g/kg EtOH + flibanserin 100 mg</td>
<td>Two 12 oz cans of beer containing 5% alcohol content</td>
</tr>
<tr>
<td></td>
<td>B. 0.8 g/kg EtOH + placebo</td>
<td>Two 5 oz glasses of wine containing 12% alcohol content</td>
</tr>
<tr>
<td></td>
<td>C. 0.4 g/kg EtOH + flibanserin 100 mg</td>
<td>Two 1.5 oz shots of 80-proof spirit</td>
</tr>
<tr>
<td></td>
<td>D. 0.4 g/kg EtOH + placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E. Flibanserin 100 mg</td>
<td></td>
</tr>
<tr>
<td>• Mean age: 31 years (21-52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fasted for 10 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ate a light breakfast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Administered study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Given up to 10 minutes to ingest liquid solution (orange juice or ethanol [EtOH] + orange juice)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data on file: Sprout Pharmaceuticals, Inc.
This led to REMS

**WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS**

**Contraindicated With Alcohol**
The use of flibanserin and alcohol increases the risk of severe hypotension and syncope. Therefore, alcohol use is contraindicated in patients taking flibanserin. Before prescribing flibanserin, assess the likelihood of the patient abstaining from alcohol, taking into account the patient’s current and past drinking behavior, and other pertinent social and medical history. Because of the increased risk of hypotension and syncope due to an interaction with alcohol, flibanserin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the flibanserin REMS Program.

**Contraindicated With Strong or Moderate CYP3A4 Inhibitors**
The concomitant use of flibanserin and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore, the use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking flibanserin.

**Contraindicated in Patients With Hepatic Impairment**
The use of flibanserin in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore, flibanserin is contraindicated in patients with hepatic impairment.
So what is new in terms of EtOH?

- Alcohol Challenge Study: Single-center, randomized, double-blind, single-dose crossover study

- Participants were randomly assigned to 1 of 12 sequence groups to receive each of 7 treatments

- Flibanserin 100 mg or placebo with ethanol 0.6 g/kg (~3 drinks), 0.4 g/kg (~2 drinks), or 0.2 g/kg (~1 drink), or flibanserin 100 mg only

- Primary endpoint was incidence of special interest adverse events
  - dizziness, syncope and hypotension

- Secondary endpoints included assessment of drowsiness by 100 mm visual analog scale (VAS)

- 96 women participated, avg age 31, BMI 23, equal distribution of regular EtOH use

- Results showed NO increased in HoTN and syncope

- Higher levels of EtOH and flibanserin caused MORE drowsiness

Sicaro et al, Effect of Alcohol Administered With Flibanserin on Dizziness, Syncope, and Hypotension in Healthy, Premenopausal Women WAS Prague May 2017
“there is still a concern about consuming alcohol close in time to taking Addyi but... it does not have to be avoided completely. Specifically, the boxed warning, contraindication, warnings and precautions, and adverse reactions sections of labeling are being updated to reflect that women should discontinue drinking alcohol ... two hours before taking Addyi at bedtime or to skip the Addyi... Women should not consume alcohol at least until the morning.”
What’s New?

• Up next is bremalanotide
  • Melanocortin4 receptor agonist
  • Prn use of autoinjector

• s/p Phase 3 (Reconnect Studies) in August 2016
  • Satisfying Sexual Events
  • FSFI
  • FSDS-desire scores

• A New Drug Application submitted in March 2018

• FDA acceptance June 21, 2019
What About Postmenopausal Women?

• Flibanserin has been studied in postmenopausal women (SWANN Study)
• Just as effective
• There is no FDA approved treatment for postmenopausal women
• Strongest data supports use of off label testosterone
Another Case

• 38 yo G3P2 with Stage 2A cervical cancer
• She underwent radical hysterectomy with ovarian sparing but 1 pos LN was found, thus she underwent radiation afterwards and her menses have now stopped
• She reports decreased libido, irritability and fatigue, skin changes and low energy
• She has dyspareunia and feels like she can no longer fit her partner, both trying to get in and then getting in all the way
• She is worried her partner will leave her over these changes, feels like her oncologist have been no help and is wondering if there is anything that can be done
What are the Issues?

• **Menopausal symptoms**
  - What is safe to use for women with cancer?
  - Does the kind of cancer matter?
  - Does timing of initiation matter?

• **Genitourinary Syndrome of Menopause**
  - What are the treatments?
  - What is safe when someone has cancer
  - Does timing of initiation matter?

• **Dyspareunia**
  - What are the causes?
  - What treatments options are available?
  - What is the evidence?
Vulva after radical vulvectomy + radiotherapy
More than just Hormones and Moisturizers

• Lubrications
  • Water-based
  • Silicone based
  • Oil based

• Pelvic Floor Muscle Training/Vaginal dilatation
  • Use of vaginal stent to prevent vaginal stenosis and make sexual intercourse possible.
  • Limited evidence on the effect on FSD

• Topical anesthetics (lidocaine) and neuroleptics (gabapentin or amytriptyline)

• Vaginal Dilators: start 4-6 weeks after, ideally 3+/week
  • Usually recommended for vaginal scarring, or vaginal stenosis from pelvic surgery or radiation

• However, evidence for the effectiveness of dilators is limited (IIC)

• Hyperbaric Oxygen (IIIC)
  • Helps restore epithelium
Screening

• Should be done at Regular Intervals
• Can use a variety of tools
• Should include contributing factors for FSD (medical and nonmedical)
• Should include thorough assessment of medications and change in medical hx
• Should take into account age, role or relationship length and menopause

• NCCN Guidelines Sexual Health 2012
The Oncosexological Algorithm

- Pre-existing Personal Factors
- Specific Factors of Cancer and Treatments
- Individual Response/Coping
- Clinical Syndrome of Sexual Dysfunction

Bitzer ISSWSH 2014
Round table with patient and partner continued

Determine and define therapeutic objectives and aims

- Should the preexisting sexual life be reestablished as much as possible?
- Should the couple find a “new” sexuality under the changed conditions, sexual rehabilitation?
- What should change and what should stay the same?
Systemic Interventions

• **Hormone Therapy**
  - Best option for menopausal symptoms
  - Can increase sexual interest and activity
  - *No indication of increased risk of recurrence* in cervical, ovarian and vulva or any other non HR+ cancer patients
  - For HR pos breast cancer, do NOT use systemic HT
  - For endometrial cancer, there is little evidence of risk but need to discuss with oncologist

• **Importance of Psychotherapy**
  - Evidence Based improvement in sex well being in Cancer Patients

• **Engage your consultants and Referral Base**
  - Physical Therapists
  - Medical, Gyn and Radiation Oncologist

NCCN 2014
Elaboration of a therapeutic plan

Decision making taking into account

- The values and general condition of the patient
- Motivation and aim of treatment (rehabilitation)
- The conditioning factors of the problem

Analgesics
Physical Therapy;
Dilatation
Local estrogen
Moisturizers
Systemic hormonal treatment
Antiinflammatory treatment
Antidepressants

Supportive Therapy
Psychotherapy
Couple Therapy
Communication
Conflicts
Coping Counselling
Psychosexual interventions
Sensate Focus

Individual therapeutic strategy
Thank You For Your Time