Sexual Health in Female Cancer Survivors

Oncology Survivorship in Primary Care Program

October 2024

Jutta Deininger WHNP, DNP

knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

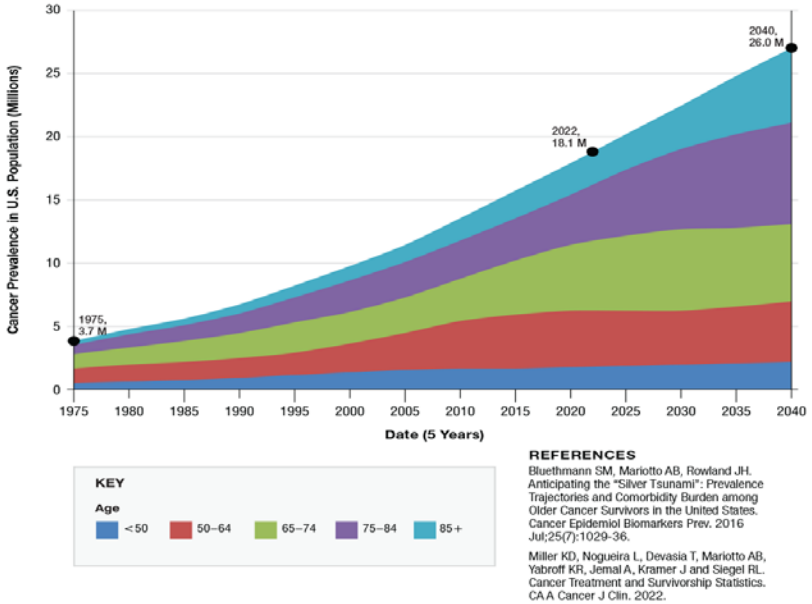
Today's Agenda

1. Scope of the sexual health problem
2. Barriers to treatment
3. Screening tools
4. Effects of cancer treatment on sexual health
5. Treatment options
6. Resources and appendix

What is the scope?

Survivorship matters

Cancer prevalence and projections in U.S. Population from 1975-2040



REFERENCES

Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36.

Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J and Siegel RL. Cancer Treatment and Survivorship Statistics. CA A Cancer J Clin. 2022.

- As of January 2022, there are 4.1 million women living with breast cancer in the USA.
- Since 2004, the incidence of invasive breast cancer is slowly rising by 0.5% per year.

Scope of the Problem

- Cancer treatment can affect Sexual Health in many different ways
- Sexual dysfunction is one of the most common long-term side effects of cancer treatment (4)
- Sexual dysfunction usually does not self-resolved (3)
- Sexual Health problems tend to worsen if not addressed (2)

For example:

- **Surgery:** loss of body parts or body integrity
- **Radiation therapy**: Loss of skin sensitivity, lymphedema
- **Chemotherapy:** Fatigue, Neuropathy, Ovarian suppression
- **Hormonal therapy:** Loss of libido, menopausal symptoms

Scope of the Problem

- Prevalence of sexual dysfunction in the USA is approximately 40%.
- It can rise to 90% in gynecological cancer survivors and affects 50-80% of prostate cancer survivors. (7,8,9)
- In the AYA population, 52% of female survivors and 32% of male survivors are reporting sexual dysfunction (6)
- 25% of female survivors of hematopoietic stem cell transplantation report cGVHD changes at the vulva/vagina (10)
- Among patients with advanced cancer, 57% of women and 68% of men rated sexual quality of life as an important factor (11)

90% of cancer survivors report that their sexual health concerns were insufficiently addressed (12)

Scope of the Problem

VICAN study*: 5 years after cancer diagnosis*

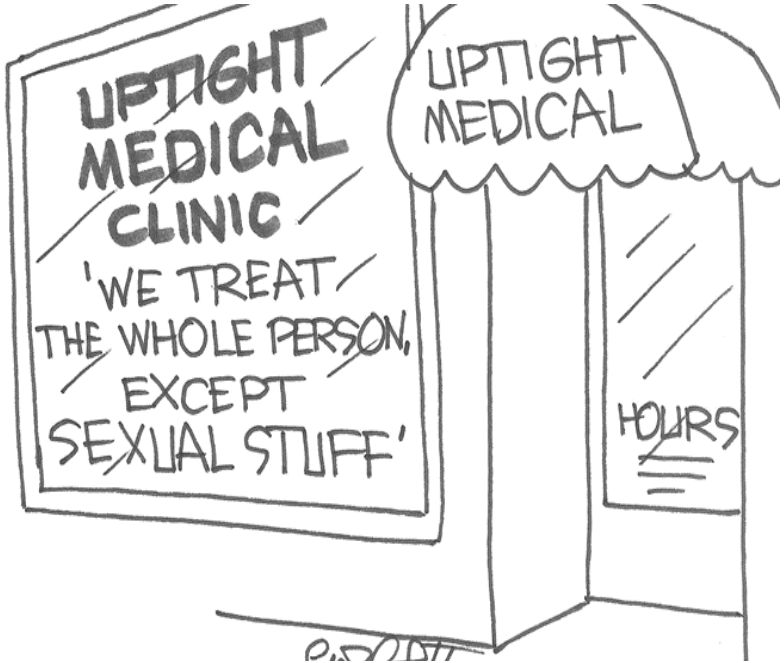
- 30.8% severe deterioration of sexual health,
- 26.5% moderate,
- 31.5% weak,
- 11.5% stable sexual health (13)

Cohort study on premenopausal BCS

- 52% reported having at least 2 sexual functions problems
- 5 and 10 years after breast cancer diagnosis sexual dysfunction remained significant in 26% and 19% (14)

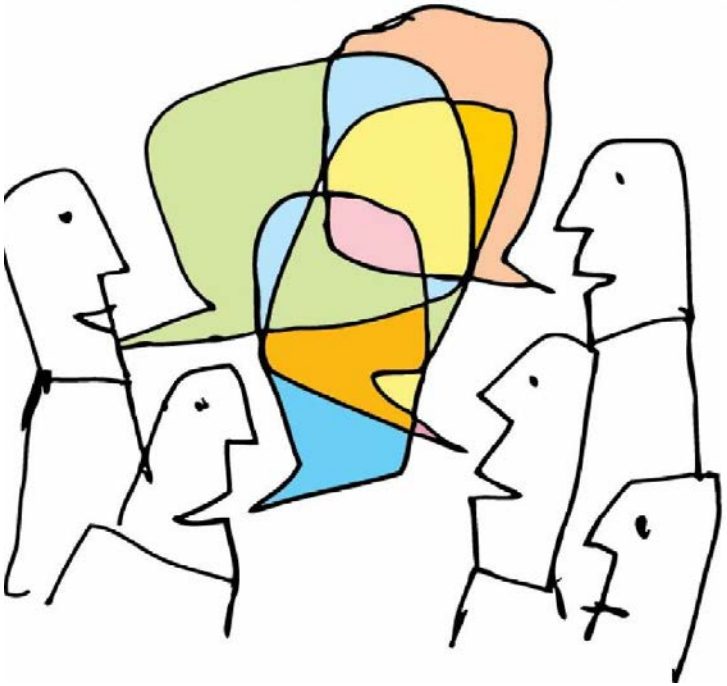
What are the barriers?

Barriers for Providers



- Lack of appropriate training
- Embarrassment
- Time pressure
- Knowledge about treatment options
- Lack of insurance coverage
- Scarcity of resources

Barriers for Patients

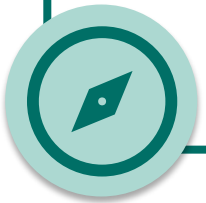


- Embarrassment
- Other symptoms are easier to describe and mention
- Feeling rushed
- Gender, culture, age of provider
- Misconception: If the provider is not talking about sexual health, there might not be any treatment and symptoms need to be accepted and endured (12)

Guidelines

NCCN guidelines

- There should be a provider-initiated discussion about sexual concerns
- Sexual Health concerns should be evaluated prior to, during, and after treatment



ASCO guidelines from 2017

- Psychosocial and/or psychosexual counseling should be offered to all patients with cancer
- Medical and treatable contributing factors should be identified and addressed first

How to screen?

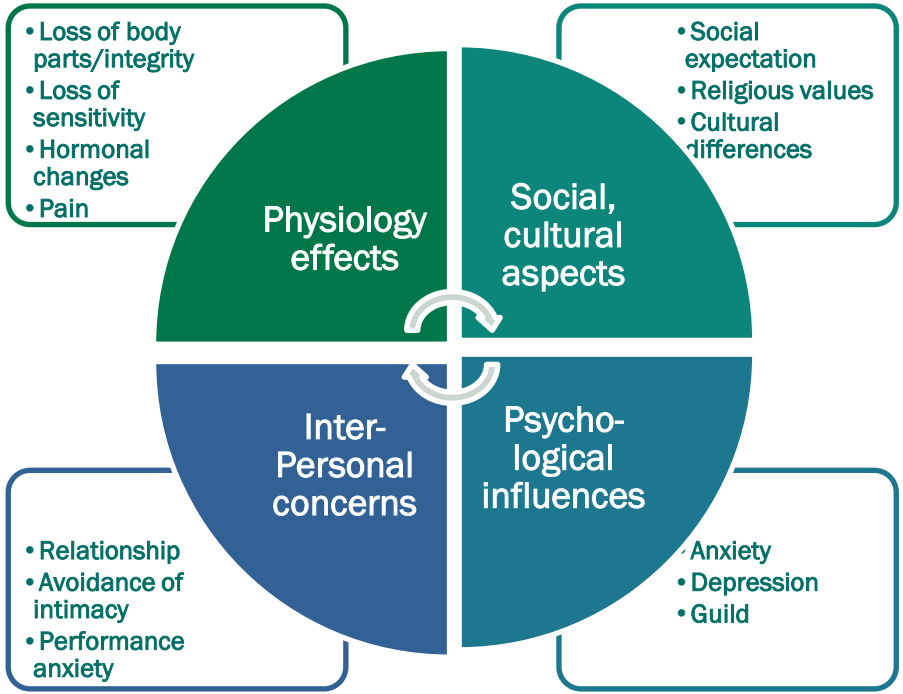
Screening Question

Screening Tools

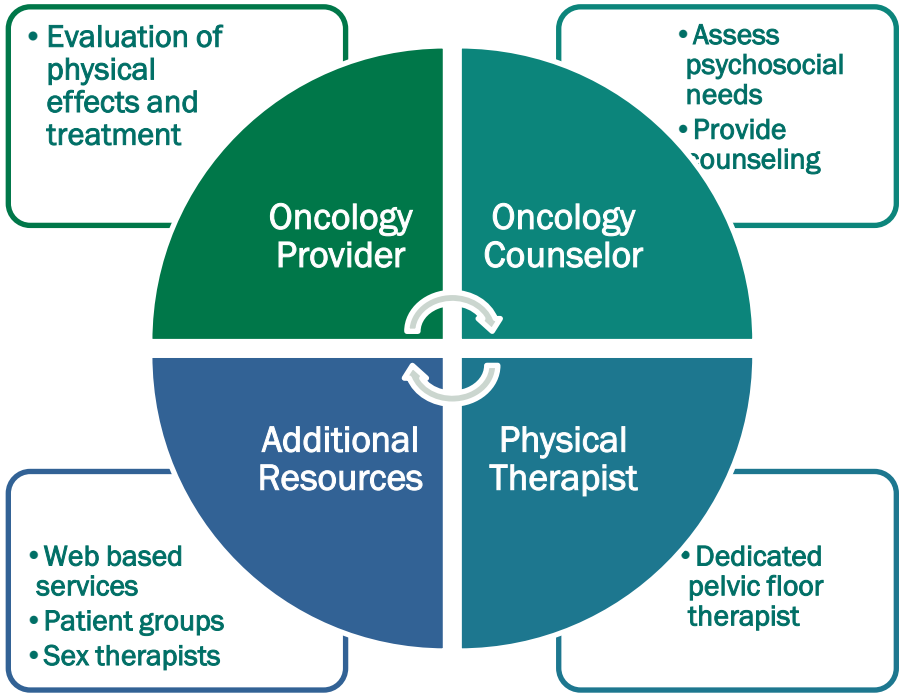
- Screening tools should be comprehensive in order to screen for all domains of sexual dysfunction according to DSM-5.
  - Desire, Arousal, Orgasm, Pain, Distress
- A review from 2013 mentioned 3 most comprehensive screening tools in breast cancer patients (15)
  - Arizona Sexual Experience scale (ASES): 5 items
  - Female Sexual Function Index (FSFI): 19 items (reflects upon sexual activity over last month)
  - Sexual Problem Scale (SPS): 9 items
- There are many other screening tests as sexual questionnaires in QOL measures (33)

Effects of Cancer Treatment

Sexual Health Dysfunction is Multifactorial

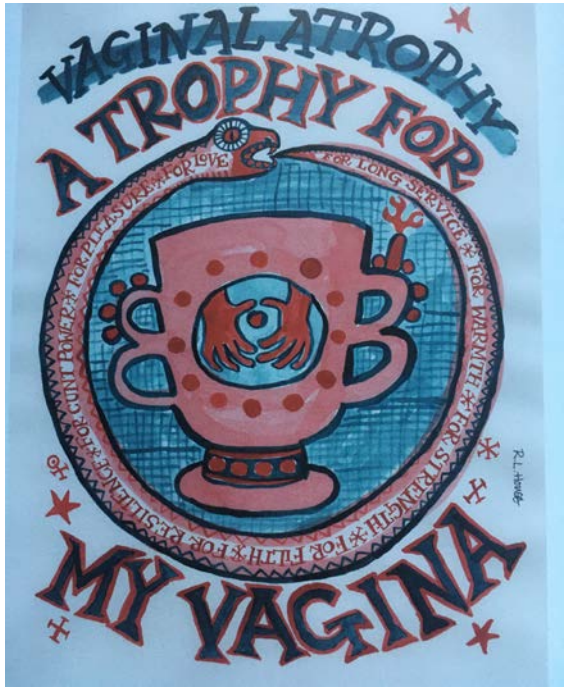


Multidisciplinary Team



GSM (Assessment and Treatment)

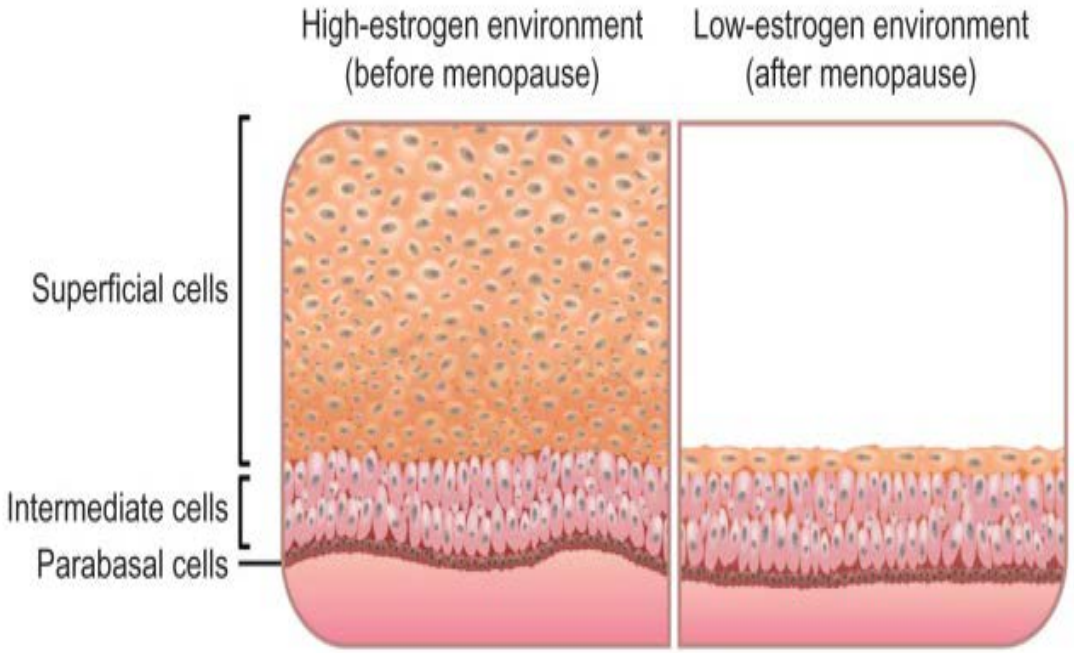
Genitourinary Symptoms of Menopause (GSM)



Lack of estrogen leads to:

- pH changes in the vagina
- Loss of elasticity
- Reduced blood supply
- Thinning of the vaginal mucosa
- Petechial bleeding in the mucosa
- Subjective symptoms:
  - Dryness,
  - Burning,
  - Dyspareunia,
  - Itching,
  - Bleeding (16,19)

Assessment of GSM



- Vaginal maturation index/Vaginal atrophy score (VAS):
  - pH
  - elasticity
  - moisture
  - wall thickness
  - epithelial integrity
- Most bothersome symptom (16)

Non-Hormonal Treatment Options for GSM

- Vaginal lubricants (variety of products: water, oil, latex-based)
- Vaginal moisturizers (variety of products, e.g., coconut oil, Hyaluronic acid, Vit E vaginal sup.)
- Physical therapy (increase of control of pelvic muscle and relaxation, increase in blood flow)
- Vaginal dilator therapy: massages of painful areas, increase elasticity, relaxation training
- Aqueous 4% lidocaine prior to penetration (16)

Outlook on Non-Hormonal Treatment for GSM

- Vaginal autologous platelet-rich plasma (a-PRP) as an intravaginal injection showed benefits in SUI, GSM and Lichen sclerosis. Studies include case serial reports and animal studies so far (35;36)
- Vasodilators: Visnadine spray applied 10 min before sexual encounter had positive effects on Female Sexual Function Index by enhancement of clitoral sensitivity (37)
- Restoring natural pH and treatment with vaginal or oral probiotics (esp. Lactobacilli) is still in debate of usefulness (35)

Pelvic Floor Muscle Therapy (PFMT) for GSM

PFMT can increase blood flow to the vagina/vulva area, improve relaxation and strength of PFM and vulvovaginal elasticity (20)

- Feasibility trial of PFMT in gynecological cancer survivors showed a high acceptance rate of treatment and 90% of patients reported improved outcome (21)
- Meta-analysis of 5 RCT and 2 retrospective cohort studies showed moderate level evidence that PFMT was beneficial for sexual function in gynecological cancer survivors (22)

Laser Treatment for GSM

- The principle is to increase collagen content and remodeling of vaginal mucosa
- There are 2 different laser treatments available
  - Non ablative photothermal Eribium: Yag laser works by causing hyperthermia of deeper layers of mucosa inducing neovascularization and collagen remodeling
  - Micro abrasive CO2 laser works by causing vaporization of water in deeper lamina propria
- Common side effects are burning and pain during procedure
- Treatments are usually 4-6 weeks apart and a baseline treatment consists of 3-4 sessions, maintenance treatment once yearly
- FDA approved but with warning of paucity of long term safety data (38)

Hormonal Treatment of GSM

Local Hormonal Treatment for GSM

- Most local estrogen preparation will not lead to increased postmenopausal levels of estrogen (<20 pg/ml)
- Multiple studies demonstrated no increased risk of developing breast or endometrial cancer in non-hormonal cancer survivors
- The exact threshold of “safe” estrogen levels in ER-positive cancer survivors is not known (16)
- ACOG recommendations for local estrogen:
  - The decision should be based on the risk of recurrence, HR type, and severity of GSM symptoms,
  - Non-hormonal approaches should be used first
  - Should be considered in conjunction with the oncologist

NAMS and ISSWSH Recommendations

Factors to consider prior to prescribing vaginal hormones in breast cancer patients

	More desirable candidates	Less desirable candidates
Stage of disease	Stage 0—2, or metastatic with limited life expectancy	Stage 3, or metastatic with extended life expectancy
Grade of disease	Low—intermediate grade	High grade
Lymph node involvement	No	Yes
Hormone receptor status	Negative	Positive
Endocrine therapy	Tamoxifen	Aromatase inhibitors
Risk of recurrence	Low	High
Time since diagnosis	Remote	Recent
Symptom severity	Severe	Mild
Nonhormone therapies	Failed	Effective
Effect on quality of life	Severe	Mild

Adapted from NAMS/ISSWSH Consensus Recommendations.[24]

Local Estrogen Therapy for GSM

4 µg estradiol preparations (Imvexxy)	*Daily for 2 weeks, then twice weekly*
7.5 µg estradiol ring (Estring)	*1 ring every 3 months*
10 µg tablets (creams can differ more in dosage) (Vagifem)	*Daily for 2 weeks, then twice weekly*

Local DHEA Therapy for GSM

- Goal of Aromatase Inhibitor (AI) treatment is to keep estradiol levels at a minimum. Even local estrogen could affect this goal.
- Vaginal DHEA preparations showed low levels of estradiol/estrone levels, well in the postmenopausal range of <5 pg/ml
- In women on AI therapy no change in estrogen levels was observed
- Testosterone levels increased slightly, androgen effect on breast cancer cells is controversial but could be protective
- Prasterone (Infrarosa) daily inserts (preferred therapy on AI) (off label for estrogen sensitive cancers) (25)

Local Testosterone Therapy

- Testosterone is used for GSM due to the richness of testosterone receptors in the vagina/vulva
- Treatment with compounded testosterone over 12 weeks showed improvement in GSM over placebo
- Few studies showed improvement of GSM in breast cancer patients under AI therapy
- Studies failed to report fully systemic androgen and estradiol levels. Therefore, local testosterone is not recommended for breast cancer survivors (16)

Systemic Hormonal Treatment in BCS

HABITS trial: women 5 years after breast cancer diagnosis and bothersome postmenopausal symptoms were randomized to HRT vs placebo

The trial was stopped early after an HR of 3.3 for breast cancer recurrence over a median follow-up of 2.1 years (25)

Summary

Systemic HRT is not recommended for ER+ breast cancer survivors at any time (26)

Selective Estrogen Receptor Modulator Ospemifene

- FDA approved for treatment of GSM in postmenopausal women
- Preclinical studies have shown anti-estrogenic effect on breast cells, but less potent than Tamoxifen or Raloxifene
- Not approved to use in breast cancer survivors or patients with high breast cancer risk
- Side effects: hot flashes and increased thromboembolic risk as other SERMs (27)
- Other SERM Tibolone showed an increase of breast cancer recurrence with a HR of 1.4 (35)

Psychosocial Effects on Sexual Health

- Decreased Libido
- Changes in body image
- Changes in self-esteem
- Avoidance of intimacy
- Partner communication and expectations
- Depression
- Anxiety (28)

FSIAD or HSDD

Female Sexual Interest/Arousal Disorder (FSIAD)

FSIAD affects about 6-13% of women in the age range of 20-70 years

Can increase with surgical or medical-induced menopause (29)

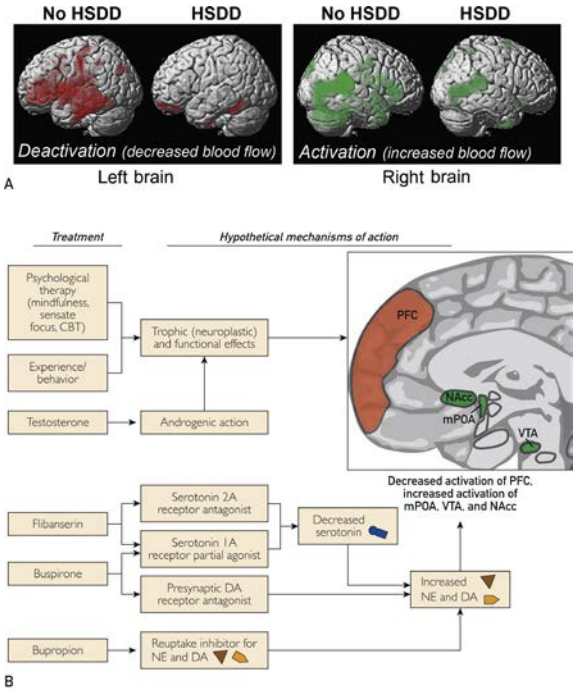
Best addressed with a *multi-disciplinary team*

- Cognitive behavior therapy
- Mindfulness
- Body awareness exercises
- Medical treatment
- Sex therapy (28)

Symptoms of FSIAD or HSDD

- Lack or loss of motivation to participate in sexual activity
- Decreased desire
- Lower response to erotic clues
- Maintaining interest or desire through sexual activity
- Symptoms should persist longer than 6 months and cause distress
- Be sure to screen for other comorbidities and check medication and drug usage with influence on sexual desire (34)

Neural Excitatory and Inhibitory Influences on HSDD



Excitation

- Dopamine
- Melanocortin
- Oxytocin
- Vasopressin
- Norepinephrine

Inhibition

- Brain opioids
- Serotonin
- Endocannabinoid systems

Hormonal activity could prime neuronal pathways

Check TSH and Prolactin to exclude endocrine interference (34)

Treatment of FSIAD with Supplements

- During arousal the endothelial Nitric Oxide Synthase (eNOS) is activated, converting Arginine and Citrulline into nitric oxide (NO)
- NO can lead to
  - Vasodilation
  - Increased lubrication
  - Relaxation of smooth muscles
- A systemic review looked at 5 RCT and 2 non-randomized trials with 6 of the seven studies reporting significant improvement in the FSFI
- Typical supplements: ArginineMax, Stronvivo, Ristela, effect after 4 weeks of treatment (30)

Pharmacological Treatment of FSIAD

Pharmacological treatment of FSIAD is based on the serotonin inhibitory pathways and dopaminergic/noradrenaline excitatory effects

Flibanserin (Addyi) reduces serotonin inhibition, FDA-approved 2015

- 100 mg daily
- Black box warning of alcohol consumption and hypotension was removed in 2019
- Often cost prohibiting (31)

Bremelanotide (Vyleesi) is a melanocortin agonist, FDA approved 2020

- Auto-injector 45 min prior to a sexual encounter
- Common side effects nausea (39%), flushing (20%), and headaches (11%)
- No more than 1 dose in 24 h, no more than 8 doses per month (32)

Testosterone

- Used in pre and postmenopausal women off-label for HSDD
- Testosterone levels should be evaluated during treatment and not exceed normal testosterone levels in women
- Testosterone levels did not predict any aspect of sexual desire. Therefore pre-treatment levels are not important
- Pellets are obsolete and transdermal gel (10% of male dose) can be used
- Common side effects are hirsutism and acne (3-8%)
- Long-term safety regarding cardiovascular disease and breast cancer are only documented in observational studies (29,34)

Other non-hormonal medical treatment options

- Bupropion
  - norepinephrine-dopamine reuptake inhibitor
  - Off-label use in HSDD
  - 150 – 400 mg daily have been studied in HSDD
  - Common side effects: tremor, dizziness, sweating, agitation, dry mouth, constipation
  - AEs lead to discontinuation in about 10 %
- Buspirone
  - serotonin 1A partial agonist
  - Off label use in HSDD
  - Side effects include headaches, dizziness, nervousness (34)

Thank you

Appendix

jdeininger@mcw.edu

Additional Resources

- http://www.cancersexnetwork.org
- http://www.menopause.org
- https://www.isswsh.org
- https://lgbtcancer.org
- www.cancercare.org/diagnosis/breast_cancer
- https://sstarnet.org

References

1. Giaquinto, A.N., Sung, H., Miller, K.D., Kramer, J.L., Newman, L.A., Minihan, A., Jemal, A. and Siegel, R.L. (2022), Breast Cancer Statistics, 2022. CA A Cancer J Clin. https://doi.org/10.3322/caac.21754
2. Jessica R Gorman, Ellie Smith, Julia H Drizin, Karen S Lyons, S Marie Harvey: Navigating sexual health in cancer survivorship: a dyadic perspective. Support Care Cancer 2020 Nov;28(11):5429-5439. doi: 10.1007/s00520-020-05396-y. Epub 2020 Mar 10.
3. Buoet, Zinger, Capitain et al:Sexual quality of life evaluation after treatment among women with breast cancer under 35 years old.Support Care Cancer 2019 Mar;27(3):879-885. doi: 10.1007/s00520-018-4374-z. Epub 2018 Aug 16
4. Bober SL, Varela VS. Sexuality in adult cancer survivors: challenges and intervention. J Clin Oncol. 2012 Oct 20;30(30):3712-9. doi: 10.1200/JCO.2012.41.7915. Epub 2012 Sep 24. PMID: 23008322.
5. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, Laumann E, Lee SW, Segraves RT. Incidence and Prevalence of Sexual Dysfunction in Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015. J Sex Med. 2016 Feb;13(2):144-52. doi: 10.1016/j.jsxm.2015.12.034. PMID: 26953829
6. Aubin S, Perez S. The clinician's toolbox: assessing the sexual impacts of cancer on adolescents and young adults with cancer (AYAC). Sex Med 2015;3:198–212
7. Laura B. Huffman,[a] Ellen M. Hartenbach,[a] Jeanne Carter,[b,c] Joanne K. Rash,[a] and David M. Kushner[a.] Maintaining Sexual Health throughout Gynecologic Cancer Survivorship: A Comprehensive Review and Clinical Guide. Gynecol Oncol. 2016 Feb; 140(2): 359–368.
8. Reese JB, Sorice K, Beach MC, Porter LS, Tulsky JA, Daly MB, Lepore SJ. Patient-provider communication about sexual concerns in cancer: a systematic review. J Cancer Surviv 2017; 11:175-88.
9. Sanchez Varela V, Zhou ES, Bober SL. Management of sexual problems in cancer patients and survivors. Curr Probl Cancer 2013;37:319–52
10. Machado,A., Hamerschlak,N., Rodrigues et al.: Female genital tract chronic graft versus host disease. A narrative review. Hematology, Transfusion and Cell Therapy, 2019 41 (1), 69-75
11. AU Kelemen A, Cagle J, Groninger H . Screening for Intimacy Concerns in a Palliative Care Population: Findings from a Pilot Study. J Palliat Med. 2016 Oct;19(10):1102-1105.
12. Reese JB, Sorice K, Beach MC, Porter LS, Tulsky JA, Daly MB, Lepore SJ. Patient-provider communication about sexual concerns in cancer: a systematic review. J Cancer Surviv 2017; 11:175-88.

References

13. Seguin L, Touzani R, Bouhnik AD, Charif AB, Marino P, Bendiane MK, Gonçalves A, Gravis G, Mancini J. Deterioration of Sexual Health in Cancer Survivors Five Years after Diagnosis: Data from the French National Prospective VICAN Survey. Cancers (Basel). 2020 Nov 20;12(11):3453. doi: 10.3390/cancers12113453. PMID: 33233583; PMCID: PMC7699784.
14. Buoet, Zinger, Capitain et al:Sexual quality of life evaluation after treatment among women with breast cancer under 35 years old.Support Care Cancer 2019 Mar;27(3):879-885. doi: 10.1007/s00520-018-4374-z. Epub 2018 Aug 16.
15. Bartula I, Sherman KA. Screening for sexual dysfunction in women diagnosed with breast cancer: systematic review and recommendations. Breast Cancer Res Treat. 2013 Sep;141(2):173-85. doi: 10.1007/s10549-013-2685-9. Epub 2013 Sep 8. PMID: 24013707; PMCID: PMC3824351.
16. Crean-Tate KK, Faubion SS, Pederson HJ, Vencill JA, Batur P. Management of genitourinary syndrome of menopause in female cancer patients: a focus on vaginal hormonal therapy. Am J Obstet Gynecol. 2020 Feb;222(2):103-113. doi: 10.1016/j.ajog.2019.08.043. Epub 2019 Aug 29. PMID: 31473229.
17. Quick AM, Dockter T, Le-Rademacher J, Salani R, Hudson C, Hundley A, Terstriep S, Streicher L, Faubion S, Loprinzi CL, Coleman JS, Wang KC, Lustberg M. Pilot study of fractional CO_2 laser therapy for genitourinary syndrome of menopause in gynecologic cancer survivors. Maturitas. 2021 Feb;144:37-44. doi: 10.1016/j.maturitas.2020.10.018. Epub 2020 Dec 2. PMID: 33358206; PMCID: PMC7773136
18. Paraiso MFR, Ferrando CA, Sokol ER, Rardin CR, Matthews CA, Karram MM, Iglesia CB. A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. Menopause. 2020 Jan;27(1):50-56. doi: 10.1097/GME.0000000000001416. PMID: 31574047.
19. Goetsch MF, Garg B, Lillemon J, Clark AL. Where does postmenopausal dyspareunia hurt? A cross-sectional report. Menopause. 2022 Jun 1;29(6):646-653. doi: 10.1097/GME.0000000000001956. PMID: 35231008.
20. Mercier J, Morin M, Tang A, Reichetzer B, Lemieux MC, Samir K, Zaki D, Gougeon F, Dumoulin C. Pelvic floor muscle training: mechanisms of action for the improvement of genitourinary syndrome of menopause. Climacteric. 2020 Oct;23(5):468-473. doi: 10.1080/13697137.2020.1724942.
21. Cyr MP, Dumoulin C, Bessette P, Pina A, Gotlieb WH, Lapointe-Milot K, Mayrand MH, Morin M. Feasibility, acceptability and effects of multimodal pelvic floor physical therapy for gynecological cancer survivors suffering from painful sexual intercourse: A multicenter prospective interventional study. Gynecol Oncol. 2020 Dec;159(3):778-784. doi: 10.1016/j.ygyno.2020.09.001. Epub 2020 Oct 1. PMID: 33010968.
22. Brennen R, Lin KY, Denehy L, Frawley HC. The Effect of Pelvic Floor Muscle Interventions on Pelvic Floor Dysfunction After Gynecological Cancer Treatment: A Systematic Review. Phys Ther. 2020 Aug 12;100(8):1357-1371. doi: 10.1093/ptj/pzaa081. PMID: 32367126.

References

23. ACOG Committee Opinion No. 659 Summary: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. Obstet Gynecol. 2016 Mar;127(3):618-619. doi: 10.1097/AOG.0000000000001349. PMID: 26901332.
24. Barton DL, Shuster LT, Dockter T, et al. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). *Support Care Cancer*. 2018;26(4):1335-1343. doi:10.1007/s00520-017-3960-9
25. Holmqvist M, Maenpaa J; HABITS Study Group. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst. 2008 Apr 2;100(7):475-82. doi: 10.1093/jnci/djn058. Epub 2008 Mar 25. Erratum in: J Natl Cancer Inst. 2008 May 7;100(9):685. Maenpa, Johanna [corrected to Maenpaa, Johanna]. PMID: 18364505.
26. Deli T, Orosz M, Jakab A. Hormone Replacement Therapy in Cancer Survivors - Review of the Literature. *Pathol Oncol Res*. 2020;26(1):63-78. doi:10.1007/s12253-018-00569-x
27. Kagan R, Kellogg-Spadt S, Parish SJ. Practical Treatment Considerations in the Management of Genitourinary Syndrome of Menopause. *Drugs Aging*. 2019;36(10):897-908. doi:10.1007/s40266-019-00700
28. Franzoi MA, Agostinetto E, Perachino M, Del Mastro L, de Azambuja E, Vaz-Luis I, Partridge AH, Lambertini M. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol. 2021 Jul;22(7):e303-e313. doi: 10.1016/S1470-2045(20)30666-5. Epub 2021 Apr 20. PMID: 33891888.
29. Parish SJ, Simon JA, Davis SR, Giraldi A, Goldstein I, Goldstein SW, Kim NN, Kingsberg SA, Morgentaler A, Nappi RE, Park K, Stuenkel CA, Traish AM, Vignozzi L. International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. J Sex Med. 2021 May;18(5):849-867. doi: 10.1016/j.jsxm.2020.10.009. Epub 2021 Apr 1. PMID: 33814355.
30. Cieri-Hutcherson NE, Jaenecke A, Bahia A, Lucas D, Oluloro A, Stimmel L, Hutcherson TC. Systematic Review of l-Arginine for the Treatment of Hypoactive Sexual Desire Disorder and Related Conditions in Women. Pharmacy (Basel). 2021 Mar 27;9(2):71. doi: 10.3390/pharmacy9020071. PMID: 33801678; PMCID: PMC8103282.

References

31. Parish SJ, Hahn SR. Hypoactive Sexual Desire Disorder: A Review of Epidemiology, Biopsychology, Diagnosis, and Treatment. Sex Med Rev. 2016 Apr;4(2):103-120. doi: 10.1016/j.sxmr.2015.11.009. Epub 2016 Feb 6. PMID: 27872021.

32. Mayer D, Lynch SE. Bremelanotide: New Drug Approved for Treating Hypoactive Sexual Desire Disorder. Ann Pharmacother. 2020 Jul;54(7):684-690 doi: 10.1177/1060028019899152. Epub 2020 Jan 1. PMID: 31893927.

33. Jeffery DD, Barbera L, Andersen BL, Siston AK, Jhingran A, Baron SR, Reese JB, Coady DJ, Carter J, Flynn KE. Self-Reported Sexual Function Measures Administered to Female Cancer Patients: A Systematic Review, 2008-2014. J Psychosoc Oncol. 2015;33(4):433-66. doi: 10.1080/07347332.2015.1046012. PMID: 25997102; PMCID: PMC4992993.

34 Goldstein I, Kim NN, Clayton AH, DeRogatis LR, Giraldi A, Parish SJ, Pfaus J, Simon JA, Kingsberg SA, Meston C, Stahl SM, Wallen K, Worsley R. Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review. Mayo Clin Proc. 2017 Jan;92(1):114-128. doi: 10.1016/j.mayocp.2016.09.018. Epub 2016 Dec 1. PMID: 27916394.

35 Merlino L, D'Ovidio G, Matys V, Piccioni MG, Porpora MG, Senatori R, Viscardi MF, Vitale A, Della Rocca C, On Behalf Of Policlinico Umberto I Collaborators. Therapeutic Choices for Genitourinary Syndrome of Menopause (GSM) in Breast Cancer Survivors: A Systematic Review and Update. Pharmaceuticals (Basel). 2023 Apr 6;16(4):550. doi: 10.3390/ph16040550. PMID: 37111307; PMCID: PMC10142093.

36 Prodromidou A, Grigoriadis T, Athanasiou S. Platelet rich plasma for the management of urogynecological disorders: the current evidence. Curr Opin Obstet Gynecol. 2022 Dec 1;34(6):396-401. doi: 10.1097/GCO.0000000000000820. Epub 2022 Aug 17. PMID: 36036461..

37 Bernorio R, Piloni S, Mori G, Prunas A, Bosoni D, Nappi RE. Efficacy and tolerability of a spray formulation containing Visnadine in women self-reporting sexual symptoms: a randomized double-blind placebo-controlled pilot study. J Endocrinol Invest. 2018 Jun;41(6):729-737. doi: 10.1007/s40618-017-0801-0. Epub 2017 Dec 11. PMID: 29230716.

38 Benini V, Ruffolo AF, Casiraghi A, Degliuomini RS, Frigerio M, Braga A, Serati M, Torella M, Candiani M, Salvatore S. New Innovations for the Treatment of Vulvovaginal Atrophy: An Up-to-Date Review. Medicina (Kaunas). 2022 Jun 6;58(6):770. doi: 10.3390/medicina58060770. PMID: 35744033; PMCID: PMC9230595.