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Guidelines Breast
Version 2023.1E

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FORSCHEN
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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Gynecological Issues in Breast Cancer Patients



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Gynecologic Issues in Breast Cancer Patients

- **Versions 2015–2022:**

Albert / Bauerfeind / Blohmer/ Fersis / Gerber / Hanf / Huober/
Loibl / Maas / Mundhenke/ Reimer / Rody / Scharl / Thill /
Thomssen / Witzel

- **Version 2023:**

Fehm / Stickeler

Screened data bases:

Pubmed	2009 –2022
ASCO	2009 - 2022
SABCS	2009 - 2022

Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

Systemic hormone (replacement-) therapy

- Endocrine responsive disease (ER pos.)
 - Combined treatment TAM plus low dose HT
- Endocrine non-responsive disease (ER neg.)
- Tibolone

Topical vaginal application of

- Estriol (E3 0.03 mg as treatment course*)
- DHEA locally
- Testosterone locally
- Estradiol (E2) during AI therapy

Oxford		
LoE	GR	AGO
1a	B	-
2b	B	+/-
1a	B	+/-
1b	A	--
2b	B	+/-
2b	B	-
2b	B	-
4	C	-

* 4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week – Note: Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred, see slide „Sexual Health“

Endocrine responsive disease

1. Paggio F, Del Mastro L, Bruzzzone M et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. Breast Cancer Res Treat. 2022 191(2):269-72.
1. Fahlén M: Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. Eur J Cancer. 2013 Jan;49(1):52-9.
2. Holmberg L: Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst 100:475-82, 2008.
3. Lupo M, Dains JE, Madsen LT. Hormone Replacement Therapy: An Increased Risk of Recurrence and Mortality for Breast Cancer Patients? J Adv Pract Oncol. 2015 Jul-Aug;6(4):322-30. Epub 2015 Jul
4. Mudhune GH, Armour M, McBride KA: Safety of menopausal hormone therapy in breast cancer survivors older than fifty at diagnosis: A systematic review and meta-analysis. Breast 2019, 47:43-55.
5. Wang Y, Lewin N, Qaoud Y et al. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. Breast. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002. Epub 2018 May 12.
6. Luo J, Cochrane B B, Wactawski-Wende J. Effects of menopausal hormone therapy on ductal carcinoma in situ of the breast. Breast Cancer Res Treat. 2013;137:915–925.

Endocrine non-responsive disease

1. Wang Y, Lewin N, Qaoud Y et al. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. *Breast*. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002. Epub 2018 May 12.

Endocrine responsive disease: combined treatment TAM plus low-dose-HT

1. Kuhle CL, Kapoor E, Sood R et al.: Menopausal hormone therapy in cancer survivors: A narrative review of the literature. *Maturitas*. 2016 Oct;92:86-96.

Tibolone

1. Kenemans P, Bundred NJ, Foidart J et al.; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol*. 2009 Feb;10(2):135-46.
2. Sismondi P., Kimmig R., Kubista E. et al.: Effects of Tibolone on climacteric symptoms and quality of life in breast cancer patients—Data from LIBERATE trial. *Maturitas*. 2011;70:365–372.
3. Bundred NJ: Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. *Breast Cancer Res*. 2012 Jan 17;14(1):R13.

Ospemifene

1. Goldstein SR, Bachmann GA, Koninckx P et al.; Ospemifene Study Group. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. *Climacteric*. 2014 Apr;17(2):173-82.
2. Cagnacci A, Xholli A, Venier M. Ospemifene in the Management of Vulvar and Vaginal Atrophy: Focus on the Assessment of Patient Acceptability and Ease of Use. *Patient Prefer Adherence*. 2020 Jan 10;14:55-62.

Topical Vaginal Application:

1. Biglia N, Peano E, Sgandurra P, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. *Gynecol Endocrinol* 2010;26(6):404–12
2. Le Ray I., Dell’Aniello S., Bonnetain F. et al.: Local estrogen therapy and risk of breast cancer recurrence among hormone treated patients: A nested case-control study. *Breast Cancer Res. Treat*. 2012;135:603–609.
3. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause:

new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Climacteric* 2014 Oct;17(5):557-63

4. Buchholz S, Mögele M, Lintermans A et al.: Vaginal estriol-lactobacilli combination and quality of life in endocrine-treated breast cancer. *Climacteric*. 2015;18(2):252-9.
5. Donders G, Belle G, Neven P et al.: Effect of ultra-low-dose estriol and lactobacilli vaginal tablets (Gynoflor®) on inflammatory and infectious markers of the vaginal ecosystem in postmenopausal women with breast cancer on aromatase inhibitors. *Eur J Clin Microbiol Infect Dis* (2015) 34:2023–2028
6. Mazzarello S1, Hutton B, Ibrahim MF et al.: Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials. *Breast Cancer Res Treat*. 2015 Jul;152(1):1-8.
7. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Farrell R. ACOG Committee Opinion No. 659: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. *Obstet Gynecol*. 2016 Mar;127(3):e93-6
8. Melisko ME, Goldman ME, Hwang J et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol*. 2017; 3(3):313-319.
9. Barton DL, Shuster LT, Dockter T et al. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). *Support Care Cancer*. 2018 Apr;26(4):1335-1343.
10. Simon JA, Goldstein I, Kim NN et al. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause*. 2018 Jul;25(7):837-847.
11. Villa P, Tagliaferri V, Amar ID et al. Local ultra-low-dose estriol gel treatment of vulvo-vaginal atrophy: efficacy and safety of long-term treatment. *Gynecol Endocrinol*. 2020 Jun;36(6):535-539.
12. The North American Menopause Society (NAMS). The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020 Sep;27(9):976-992.
13. Jain AL, Jamy O, Mullins J et al. Usefulness of patient-reported outcomes to assess the effectiveness of topical hormonal therapy for gynecologic symptoms after antihormonal treatment for breast cancer. *Proc (Bayl Univ Med Cent)*. 2020 Apr 7;33(3):331-335.
14. Hirschberg AL, Sánchez-Rovira P, Presa-Lorite J et al. Efficacy and safety of ultra-low dose 0.005% estriol vaginal gel for the treatment of vulvovaginal atrophy in postmenopausal women with early breast cancer treated with nonsteroidal aromatase

inhibitors: a phase II, randomized, double-blind, placebo-controlled trial. Menopause. 2020 May;27(5):526-534.

Further Medical Approaches to Reduce Menopausal Symptoms I

Medical approaches* (reduction of hot flashes)	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients <ul style="list-style-type: none"> Venlafaxine Desvenlafaxine, Sertraline, Escitalopram Gabapentin (patients using TAM) Oxybutynine (2.5 mg / 5 mg) Pregabalin Clonidine 0.05-0.15 mg/die (patients using TAM) MPA (i.m. 500 mg single shot) (most potent, but endocrine agent!) Vitamin E Omega-3 fatty acids 	1a 1b 1a 1b 1b 2a 1b 1b 1b	A A A A A B A A A	+ +/- + +/- +/- +/- +/- - +/-
Medical approaches (other treatment goals) <ul style="list-style-type: none"> Melatonin (improvement in sleep quality) Duloxetine (treating arthralgias while on AI) 	2b 1b	C B	+ +

* Note: Substantial placebo-effect has been proven (23-57%) **LoE 1b A +**

- Chubak J, Bowles EJ, Yu O, Buist DS et al.: Breast cancer recurrence in relation to antidepressant use. Cancer Causes Control. 2016 Jan;27(1):125-36.
- Haque R, Shi J, Schottinger JE et al.: Tamoxifen and Antidepressant Drug Interaction in a Cohort of 16 887 Breast Cancer Survivors. J Natl Cancer Inst. 2015 Dec 1;108(3).
- L'Espérance S: Pharmacological and non-hormonal treatment of hot flashes in breast cancer survivors: CEPO review and recommendations. Support Care Cancer. 2013 May;21(5):1461-74
- Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ. 2010;340:c693.
- Bordeleau L: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52.
- Wiśniewska I, Jochymek B, Lenart-Lipińska M et al.: The pharmacological and hormonal therapy of hot flashes in breast cancer survivors. Breast Cancer. 2016 Mar;23(2):178-82.
- Antoine C, Ameye L, Paesmans M et al.: Treatment of climacteric symptoms in breast cancer patients: a retrospective study from a medication databank. Maturitas. 2014 Jul;78(3):228-32.
- Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015;10;4:65.

9. Leon-Ferre RA, Majithia N, Loprinzi CL. Management of hot flashes in women with breast cancer receiving ovarian function suppression. *Cancer Treat Rev*. 2017 Jan;52:82-90.

SSRI

1. Shams T1, Firwana B, Habib F et al.: SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. *J Gen Intern Med*. 2014 Jan;29(1):204-13.

Venlafaxine

1. Ramaswami R, Villarreal MD, Pitta DM et al.: Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2015 Jul;152(2):231-7.
2. Boekhout AH, Vincent AD, Dalesio OB et al: Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2011 Oct 10;29(29):3862-8.
3. Bordeleau L, Pritchard KI, Loprinzi CL et al: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *J Clin Oncol*. 2010 Dec 10;28(35):5147-52.

Desvenlafaxine

1. Archer DF, Dupont CM, Constantine GD et al.: Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety. *Am J Obstet Gynecol*. 2009;200(3):238 e231–238 e210.
2. Speroff L, Gass M, Constantine G et al.: Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol*. 2008;111(1):77–87.
3. Deecher DC, Alf inito PD, Leventhal L et al.: Alleviation of thermoregulatory dysfunction with the new serotonin and norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized rodent models. *Endocrinology*. 2007;148(3):1376–1383.

Paroxetine

1. Simon JA, Portman DJ, Kaunitz AM et al.: Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause*. 2013 Oct;20(10):1027-35. doi: 10.1097/GME.0b013e3182a66aa7.

Fluoxetine

1. Loprinzi CL, Sloan J, Stearns V et al.: Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol. 2009;27(17):2831–2837.

Citalopram

1. Barton DL, LaVasseur B, Sloan JA et al.: A phase III trial evaluating three doses of citalopram for hot flashes: NCCTG trial N05C9. J Clin Oncol. 2008;26(20):9538.
2. Kalay AE, Demir B, Haberal A et al.: Efficacy of citalopram on climacteric symptoms. Menopause. 2007;14(2):223–229.

Gabapentin

1. Bordeleau L, Pritchard KI, Loprinzi CL et al: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52
2. Shan D, Zou L, Liu X, et al. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020 Jun;222(6):564-579.e12.

Pregabalin

1. Loprinzi CL, Qin R, Baclueva EP et al.: Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. J Clin Oncol. 2010;28(4):641–647.

Clonidine

1. Drewe J, Bucher KA, Zahner CA.: systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015 Feb 10;4:65. doi: 10.1186/s40064-015-0808-y. eCollection 2015.
2. Boekhout AH, Vincent AD, Dalesio OB et al: Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2011 Oct 10;29(29):3862-8
3. Friedman GD, Udaltsova N, Habel LA: Norepinephrine antagonists and cancer risk. Int J Cancer 2011. 128(3):737–738, doi:10.1002/ijc.25351 (Clonidine)
4. Burbos N, Morris EP. Menopausal symptoms. BMJ Clin Evid. 2011 Jun 15;2011:0804.

Oxybutynin

1. Leon-Ferre RA, Novotny PJ, Wolfe EG et al. Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603). JNCI Cancer Spectr. 2019 Oct 21;4(1):pkz088.
2. Simon JA, Gaines T, LaGuardia KD; Extended-Release Oxybutynin Therapy for VMS Study Group. Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause. 2016 Nov;23(11):1214-1221.

(D) MPA (depo-) (Medroxyprogesterone acetate)

1. Prior JC, Nielsen JD, Hitchcock CL et al.: Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy. Clin Sci (Lond). 2007;112(10):517–525.
2. Loprinzi CL, Levitt R, Barton D et al.: Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol. 2006 Mar 20;24(9):1409-14. Epub 2006 Feb 27.
3. Ertz-Archambault NM, Rogoff LB, Kosiorek HE et al.: Depomedroxyprogesterone acetate therapy for hot flashes in survivors of breast cancer: no unfavorable impact on recurrence and survival. Support Care Cancer. 2019 Aug 11. doi: 10.1007/s00520-019-05013-7. [Epub ahead of print]

Vitamine E

1. Rada G: Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review). The Cochrane Library 2010, Issue 9.
2. Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat. 2009 Jun;115(3):437-52.
3. Biglia N, Sgandurra P, Peano E et al.: Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric. 2009 Aug;12(4):310-8.

Omega 3-Fettsäuren

1. Lustberg M'B, Orchard TS, Reinbolt R et al. Randomized placebo-controlled pilot trial of omega 3 fatty acids for prevention of aromatase inhibitor-induced musculoskeletal pain. Breast Cancer Res Treat. 2018 Feb;167(3) 709-718. doi: 10.1007/s10549-017-4559-z. Epub 2017 Nov 3.

Melatonin

1. Chen WY, Giobbie-Hurder A, Gantman K et al.: A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. *Breast Cancer Res Treat* 2014. 145(2):381–388, doi:10.1007/s10549-014-2944-4

Duloxetine

1. Henry NL, Unger JM, Schott AF et al. Randomized, Multicenter, Placebo-Controlled Clinical Trial of Duloxetine Versus Placebo for Aromatase Inhibitor-Associated Arthralgias in Early-Stage Breast Cancer: SWOG S1202. *J Clin Oncol*. 2018 Feb 1;36(4):326-332. doi: 10.1200/JCO.2017.74.6651. Epub 2017 Nov 14.

CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

During anti-cancer treatment: Beware of drug interactions!

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Soy-derived phytoestrogens – isoflavonoids* <ul style="list-style-type: none"> Hot flushes Sleep disturbance Topical vaginal application 	1b 1b 1b	B B B	- +/- +/-
<ul style="list-style-type: none"> Red Clover isoflavonoids* <ul style="list-style-type: none"> Hot flushes, sleep disturbance 	1b	B	+/-
<ul style="list-style-type: none"> Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses, no effect on hot flashes) 	2b	B	+/-
<ul style="list-style-type: none"> Black Cohosh for hot flushes 	1b	B	+/-
<ul style="list-style-type: none"> Black cohosh + St. John's Wort (fixed combination) 	1b	B	+/-
<ul style="list-style-type: none"> St. John's Wort (pharmacokinetic interference with endocrine therapy, cytotoxic drugs, and tyrosin kinase inhibitors) 	1b	B	+/-
<ul style="list-style-type: none"> Ginseng root (Panax ginseng or P. quinquefolius) 	1b	B	-
<ul style="list-style-type: none"> Bromelain + Papain + Selenium + Lectin (for AI induced joint symptoms) 	3b	B	+
<ul style="list-style-type: none"> Homeopathic medicine to reduce hot flushes (consider placebo-effect) 	1b	B	+/-

* might stimulate BC, especially in endocrine responsive disease

1. Roberts H. Safety of herbal medicinal products in women with breast cancer. *Maturitas*. 2010;66(4):363-9.
2. Ma H: Estrogenic botanical supplements, health-related quality of life, fatigue, and hormone-related symptoms in breast cancer survivors: a HEAL study report. *BMC Complement Altern Med*. 2011;11:109.
3. Kim W, Lee WB, Lee JW et al.: Traditional herbal medicine as adjunctive therapy for breast cancer: A systematic review. *Complement Ther Med*. 2015 Aug;23(4):626-32. doi: 10.1016/j.ctim.2015.03.011.
4. Lethaby A, Marjoribanks J, Kronenberg F et al.: Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev*. 2013 Dec 10;(12):CD001395. doi: 10.1002/14651858.CD001395.pub4.

Soy- derieved isoflavonoids

Red clover-derived isoflavonoids

1. Chen MN: Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric*. 2015 Apr;18(2):260-9.
2. Lethaby A: Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev*. 2013 Dec 10;12:CD001395.
3. Fritz H, Seely D, Flower G et al.: red clover, and isoflavones and breast cancer: a systematic review. *PLoS One*. 2013 Nov 28;8(11):e81968.
4. Ghazanfarpour M, Sadeghi R, Latifnejad Roudsari R et al.: Effects of red clover on hot flash and circulating hormone concentrations

in menopausal women: a systematic review and meta-analysis. *Avicenna J Phytomed*. 2015 Nov-Dec;5(6):498-511.

5. Shakeri F: Effectiveness of red clover in alleviating of menopausal symptoms: A 12-week randomized, controlled trial. *Climacteric*. 2015;18(4):568-73.
6. Ghazanfarpour M, Latifnejad Roudsari R, Treglia G et al.: Topical administration of isoflavones for treatment of vaginal symptoms in postmenopausal women: A systematic review of randomised controlled trials. *J Obstet Gynaecol*. 2015 Nov;35(8):783-7.
7. Ghazanfarpour M, Sadeghi R, Roudsari RL. The application of soy isoflavones for subjective symptoms and objective signs of vaginal atrophy in menopause: A systematic review of randomised controlled trials. *J Obstet Gynaecol*. 2016;36(2):160-71.
8. Ribeiro AE, Monteiro NES, Moraes AVG et al. Can the use of probiotics in association with isoflavone improve the symptoms of genitourinary syndrome of menopause? Results from a randomized controlled trial. *Menopause*. 2018 Dec 10. doi: 10.1097/GME.0000000000001279. [Epub ahead of print]

Flaxseed

1. Flower G: Flax and Breast Cancer: A Systematic Review. *Integr Cancer Ther*. 2013 8;13(3):181-192.
2. Pruthi S: A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. *Menopause* 2012; 19:48-53.

Black cohosh (Cimicifuga racemosa) nor St John's Wort nor Ginseng root

1. Leach MJ: Black cohosh (Cimicifuga spp.) for menopausal symptoms. *Cochrane Database Syst Rev*. 2012; 9:CD007244.
2. Caraci F: Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. *Curr Drug Metab*. 2011 Jul 1;12(6):570-7.
3. Kim MS: Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials. *J Ginseng Res*. 2013 Mar;37(1):30-6.
4. Mehrpooya M1, Rabiee S2, Larki-Harchegani A3, Fallahian AM1, Moradi A4, Ataei S1, Javad MT5. A comparative study on the effect of "black cohosh" and "evening primrose oil" on menopausal hot flashes. *J Educ Health Promot*. 2018 Mar 1;7:36. doi: 10.4103/jehp.jehp_81_17. eCollection 2018.
5. Wobser RW, Takov V. Black Cohosh. 2020 Dec 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. PMID: 29261886.

Sodium selenite, proteolytic plant enzymes (bromelain and papain), and Lens culinaris lectin

1. Beuth J, van Leendert R, Schneider B et al.: Complementary medicine on side-effects of adjuvant hormone therapy in patients with breast cancer. *In Vivo*. 2013 Nov-Dec;27(6):869-71.

Homeopathic medicine

1. Heudel PE, Van Praagh-Doreau I, Duvert B et al.: Does a homeopathic medicine reduce hot flushes induced by adjuvant endocrine therapy in localized breast cancer patients? A multicenter randomized placebo-controlled phase III trial. *Support Care Cancer*. 2019 May;27(5):1879-1889. doi: 10.1007/s00520-018-4449-x. Epub 2018 Sep 7.

General Approaches to Reduce Menopausal Symptoms III - Integrative Oncology Aspects

General approaches:	Oxford		
	LoE	GR	AGO
▪ Physical exercise	1a	A	++
▪ Cognitive behavioral therapy (CBT), hypnosis	1a	A	++
▪ Mind body-medicine (yoga, education, counselling, mindfulness training)	1b	B	+
▪ Short interruption of endocrine therapy in case of unacceptable side effects	5	D	+
(Electro) Acupuncture			
▪ Aromatase-inhibitor treatment induced arthralgia	1a	B	+
▪ Hot flushes	2a	B	+
▪ Anxiety, Depression	2b	B	+
▪ Sleep	2a	C	+
* as in SOLE Trial			

1. Duncan M, Moschopoulou E, Herrington E et al.: Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. BMJ Open. 2017 Nov 28;7(11):e015860.
2. Tran S, Hickey M, Saunders C et al. Nonpharmacological therapies for the management of menopausal vasomotor symptoms in breast cancer survivors. Support Care Cancer. 2020 Sep 17. doi: 10.1007/s00520-020-05754-w. Epub ahead of print. PMID: 32940768.
3. S3-Leitlinie: Peri- and Postmenopause. Diagnosis and Interventions. Guideline of the DGGG, SGGG and OEGGG (S3 Level, AWMF Registry No.015-062, January 2020). <http://www.awmf.org/leitlinien/detail/II/015-062.html>

Physical exercise

1. Duijts SF: Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. J Clin Oncol. 2012 Nov 20;30(33):4124-33.
2. Hartman SJ, Nelson SH, Myers E et al.: Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study. Cancer. 2018 Jan 1;124(1):192-202. doi: 10.1002/cncr.30987. Epub 2017 Sep 19.
3. Lahart IM, Metsios GS, Nevill AM et al.: Physical activity for women with breast cancer after adjuvant therapy. Cochrane

Mind Body Medicine

1. Buffart LM: Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 2012 Nov 27;12:559.
2. Cramer H: Characteristics of randomized controlled trials of yoga: a bibliometric analysis. *BMC Complement Altern Med*. 2014 Sep 2;14:328.
3. Haller H, Winkler MM, Klose P et al.: Mindfulness-based interventions for women with breast cancer: an updated systematic review and meta-analysis. *Acta Oncol* 2017, 56:1665-76.
4. Koch AK, Rabsilber S, Lauche R et al.: The effects of yoga and self-esteem on menopausal symptoms and quality of life in breast cancer survivors-A secondary analysis of a randomized controlled trial. *Maturitas* 2017 Nov;105:95-99. doi: 10.1016/j.maturitas.2017.05.008. Epub 2017 May 13.
5. Goldstein KM, Shepherd-Banigan M, Coeytaux RR et al.: Use of mindfulness, meditation and relaxation to treat vasomotor symptoms. *Climacteric*. 2017;20(2):178-82.
6. Stefanopoulou E, Grunfeld EA. Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review. *J Psychosom Obstet Gynaecol*. 2017;38(3):210-25
7. Tao WW, Tao XM, Song CL. Effects of non-pharmacological supportive care for hot flushes in breast cancer: a meta-analysis. *Support Care Cancer*. 2017;25(7):2335-47
8. Tran S, Hickey M, Saunders C et al. Nonpharmacological therapies for the management of menopausal vasomotor symptoms in breast cancer survivors. *Support Care Cancer*. 2020 Sep 17. doi: 10.1007/s00520-020-05754-w. Epub ahead of print. PMID: 32940768.

Cognitive behavioral therapy, Hypnosis

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32940768.

Ovarian Protection with GnRHa and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

- CTx + GnRHa
(preservation of ovarian function)
(GnRHa application > 2 weeks prior to chemo-therapy,
independent of hormone receptor status)
- CTx + GnRHa
(preservation of fertility)
- Fertility preservation counselling including
referral of all potential patients to appropriate
reproductive specialists (further information
<https://fertiprotekt.com/english>; S2K Guideline Fertility
preservation in oncology)

Oxford		
LoE	GR	AGO
1a	A	+
2a	B	+/-
		++

Ovarian function protection

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Fertility preservation counselling

1. Loren AW, Mangu PB, Beck LN et al. Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2013;31(19):2500–10.
2. Peccatori FA, Azim Jr HA, Orecchia R et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–70.
3. Abe A, Kuwahara A, Iwasa T et al.: A survey on fertility management in young women of reproductive age treated with chemotherapy. Int J Clin Oncol. 2016 Dec;21(6):1183-1190.
4. Marklund A, et al. Reproductive Outcomes After Breast Cancer in Women With vs Without Fertility Preservation. JAMA Oncol. 2021 Jan 1;7(1):86-91.
5. https://register.awmf.org/assets/guidelines/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12-verlaengert.pdf

Fertility preservation and assisted reproductive therapy (ART) - Oncological safety¹-

	Oxford		
	LoE	GR	AGO
▪ Pretreatment approaches to preserve fertility			
GnRHa	1a	A	++
Cryopreservation of ovarian tissue with subsequent transplantation ²	4	D	+
Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation	2a	C	+
▪ ART after (neo-)adjuvant systemic treatment	4	C	+

¹Evidence is limited due to studies with poor quality e.g. (prospective randomized trials are not feasible)

² Risk of relapse caused by transplantation of ovarian tissue containing tumor cells from the original malignancy; Removal of transplanted ovarian tissue is necessary in patients with BRCA1/2 mutations due to increased risk of ovarian cancer

GnRH-Analogon:

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Cryopreservation of ovarian tissue:

1. Bastings L, Beerendonk CC, Westphal JR, et al. Autotransplantation of cryopreserved ovarian tissue in cancer survivors and the risk of reintroducing malignancy: a systematic review. Hum Reprod Update. 2013;19(5):483-506. doi: 10.1093/humupd/dmt020. Epub 2013 Jun 30. PMID: 23817363.
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Cryoconservation of oocytes after ovarian stimulation:

1. Luke B, Brown MB, Missmer SA et al.: Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016 ;31(1):183-9.
2. Oktay K, Turan V, Bedoschi G et al.: Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. J Clin Oncol. 2015;33(22):2424–9.
3. Arecco L, Blondeaux E, Bruzzone M, et al.. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022; 37(5):954-968. doi: 10.1093/humrep/deac035. PMID: 35220429; PMCID: PMC9071231.
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ART after treatment:

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FORSCHEN
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Oncological Safety of controlled ovarian stimulation (COS) or assisted reproductive therapy (ART)

N=15 studies including 4643 patients undergoing COS or ART (assisted reproductive therapy)

COS before starting treatment (n=11 studies):

Reduced risk of recurrence RR 0.58, 95% CI 0.46-0.73

Reduced risk of mortality RR 0.54, 95% CI 0.38-0.76

No detrimental effect on EFS 0.76, 95% CI 0.55-1.06

- Subgroup of HR positive pts. HR 0.36, 95% CI 0.20-0.65

ART after treatment (n=4 studies):

Reduced risk of recurrence (RR 0.34, 95% CI 0.17-0.70)

No detrimental effect EFS (HR 0.43, 95% CI 0.17-1.11).

Conclusion: COS at diagnosis or ART following breast cancer treatment completion does not appear to be associated with any detrimental prognostic effect in young women

Arecco et al. Human Reprod 2022

Arecco L, Blondeaux E, Bruzzone M, et al.. Safety of fertility preservation techniques before and after anticancer treatments in young women with breast cancer: a systematic review and meta-analysis. Hum Reprod. 2022 ;37(5):954-968. doi: 10.1093/humrep/deac035. PMID: 35220429; PMCID: PMC9071231.

Ovarian Protection – Synopsis of Randomized Trials

	ZORO	PROMISE	Munster et al. - US	POEMS	Option
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)	227 (126 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years	premenopausal
Treatment	goserelin	triptorelin	triptorelin	goserelin	goserelin
Start of treatment	> 2 weeks prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht	> 1 week prior to cht
Primary Endpoint	menstruation at month 6 after chemotherapy	rate of early menopause at month 12 after cht	menstruation rate within 2 years after cht	Ovarian failure at 2 yrs after cht	Amenorrhea with elevated FSH levels between 12 and 24 months
Primary objective	to detect 30% absolute increase of menstruation rate	to detect at least 20% absolute reduction in early menopause	to detect 20% difference in amenorrhea rate – from 10% to 30%		To detect 20%-25% absolute reduction in early menopause
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only independent predictive factor	Age, total cyclophosphamide dose and baseline AMH
Resumption of menses at month 12	83% with LHRH vs. 80% w/o	93% with LHRHa vs. 74% w/o	74% with LHRH vs. 68% w/o	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%	78% with LHRHa vs. 62% amenorrhea rate between month 12 and 24
Median time to restoration of menses (months)	6.1 with LHRHa vs. 6.8 w/o; p = 0.30	not reached with LHRH vs. 6.7 w/o; p = 0.07	5.8 with LHRH vs. 5.0 w/o; p = 0.58	n.d.	n.d.
Cyclophosph. dose	4600 vs. 4700 mg	4080 vs. 4008 mg	n.r.	n.a.	5940 vs. 5940 mg

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Assessment of Ovarian Reserve

Tests for fertility assessment

- Anti-Müllerian Hormone
- Antral follicle count
- FSH
- Combined test procedures for assessment of ovarian reserve*

Oxford		
LoE	GR	AGO
1b	B	+
3b	B	+
2b ^a	B	+
5	C	+

* Tests are suggested for women > 35 y and infertility for 6-12 months; the tests do not predict failure to conceive. They should be used in counselling patients and to provide a rough estimate of the fertility window. Results may decrease patient referral time to infertility centers.

AMH:

1. Anderson RA, Mansi J, Coleman RE et al.: The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer. Eur J Cancer. 2017;87:58-64
2. Fréour T, Barrière P, Masson D. Anti-müllerian hormone levels and evolution in women of reproductive age with breast cancer treated with chemotherapy. Eur J Cancer. 2017 Mar;74:1-8. doi: 10.1016/j.ejca.2016.12.008. Epub 2017 Jan 28.
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Antrale Follicle Count:

1. Sinha N, Letourneau JM, Wald K et al: Antral follicle count recovery in women with menses after treatment with and without

- gonadotropin-releasing hormone agonist use during chemotherapy for breast cancer. J Assist Reprod Genet 2018, 35:1861-8.
2. Su HI, Chung K, Sammel MD et al.: Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. Fertil Steril. 2011 Apr;95(5):1857-9.

FSH

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2. Furlanetto J, Marmé F, Seiler S, et al. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials. Eur J Cancer. 2021;152:193-203. doi: 10.1016/j.ejca.2021.04.038.

Combined tests:

1. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2020;114(6):1151-1157

Contraceptive Options for Women after Diagnosis of Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Barrier methods	5	D	+
▪ Sterilization (tubal ligation / salpingectomy / vasectomy)	5	D	+
▪ Non-hormonal intrauterine devices (IUDs)	3b	D	+
▪ Levonorgestrel-releasing IUDs	2b	C	-
▪ Removal in newly diagnosed patients	4	D	+/-
▪ Timing methods	5	D	-
▪ Injectable progestin-only contraceptives	5	D	-
▪ Progestin-only oral contraceptives	5	D	-
▪ Combined oral contraceptives	5	D	-
▪ Options of emergency contraception			
▪ Copper intrauterine device (Copper-IUD)	5	D	+
▪ Levonorgestrel, Ulipristal orally	5	D	+

Contraception (general)

1. Moormann PG, Havrilesky LJ, Giersch JM et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013 Nov 20;31(33):4188-98.
2. Lambertini M, Massarotti C, Havas et al. Contraceptive Use in Premenopausal Women With Early Breast Cancer. JAMA Netw Open. 2022;5(9)

LNG-IUDs

1. Dominick S et al: Levonogestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database syst Rev 2015; Dec 9; 12: CD007245.
2. Soini T, Hurskainen R, Grénman S et al.: Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. Acta Oncol. 2016 Feb;55(2):188-92.
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Emergency Contraception - Options after Diagnosis of Breast Cancer

1. Casay PM et al: Caring for breast cancer survivor's health and well being WJCO 2014;10: 5 (4): 693-704

Sexual Health / Vaginal Dryness

Evaluation	Oxford		
	LoE	GR	AGO
▪ Assessment of sexual dysfunction	5	D	+
▪ Use of patient-reported questionnaires	4	C	+
Therapy of dyspareunia and vaginal dryness			
▪ Psychoeducational support, group therapy, sexual counselling, marital counselling, psychotherapy	1b	B	+
▪ Topical vaginal treatment			
▪ Non-hormonal lubricants / moisturizers (also with physiotherapy)	1b	B	+
▪ Estriol (E3 0.03 mg as treatment course*)	2b	B	+/-
▪ DHEA local application	2b	B	-
▪ Testosterone local application	2b	B	-
▪ Estradiol (E2) during AI therapy	4	C	-
▪ Fractionated microablative CO ₂ -Laser / Vaginal Erbium:YAG-Laser	2a	B	+/-

* 4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week – Note: Elevated E3-blood levels only with start of therapy; oncological endpoints were not studied. Non-hormonal alternatives should be preferred.

Reviews:

1. The North American Menopause Society (NAMS). The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020 Sep;27(9):976-992.
2. Runowicz CD, Leach CR, Henry NL et al.: American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2015 Dec 7. pii: JCO.2015.64.3809

Evaluation

Sexual Complaints Screener For Women:

1. Burri A, Porst H. Preliminary Validation of a German Version of the Sexual Complaints Screener for Women in a Female Population Sample. Sex Med. 2018 Jun;6(2):123-130.
2. Rosen R, Brown C, Heiman J et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000 Apr-Jun;26(2):191-208.
3. Isidori AM, Pozza C, Esposito K et al. Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. J Sex Med. 2010 Mar;7(3):1139-46.

Treatment of vaginal dryness:

Education, Group therapy, counselation:

1. Carroll AJ, Baron SR, Carroll RA. Couple-based treatment for sexual problems following breast cancer: A review and synthesis of the literature. *Support Care Cancer*. 2016 Aug;24(8):3651-9.
2. Huynh V, Vemuru S, Hampanda K, et al. No One-Size-Fits-All: Sexual Health Education Preferences in Patients with Breast Cancer. *Ann Surg Oncol*. 2022;29(10):6238-6251.

Non-hormonal treatment:

1. Juraskova I, Jarvis S, Mok K et al. The acceptability, feasibility, and efficacy (phase I/II study) of the OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR) intervention to improve dyspareunia and alleviate sexual problems in women with breast cancer. *J Sex Med*. 2013 Oct;10(10):2549-58.

Vaginal topic treatment

1. Donders G, Belle G, Neven P et al.: Effect of ultra-low-dose estriol and lactobacilli vaginal tablets (Gynoflor®) on inflammatory and infectious markers of the vaginal ecosystem in postmenopausal women with breast cancer on aromatase inhibitors. *Eur J Clin Microbiol Infect Dis* (2015) 34:2023–2028
2. Cold S et al. Vaginal estrogens and risk of recurrence or death in women treated for estrogen receptor positive breast cancer, *European Journal of Cancer* 2015,51, S3 (Abstract)
3. Mazzarello S1, Hutton B, Ibrahim MF et al.: Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials. *Breast Cancer Res Treat*. 2015 Jul;152(1):1-8.
4. Advani P, Brewster AM, Baum GP et al.: A pilot randomized trial to prevent sexual dysfunction in postmenopausal breast cancer survivors starting adjuvant aromatase inhibitor therapy. *J Cancer Surviv*. 2017;11(4):477-85
5. Kim YH, Park S, Lee M et al.: Effect of a pH-Balanced Vaginal Gel on Dyspareunia and Sexual Function in Breast Cancer Survivors Who Were Premenopausal at Diagnosis: A Randomized Controlled Trial. *Obstet Gynecol*. 2017;129(5):870-6.
6. Melisko ME, Goldman ME, Hwang J et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol* 2017; 3(3):313-319.
7. Barton DL, Sloan JA, Shuster LT et al. Evaluating the efficacy of vaginal dehydroepiandrosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance). *Support Care Cancer*. 2018 Feb;26(2):643-650. doi: 10.1007/s00520-017-3878-2.


8. Simon JA, Goldstein I, Kim NN et al. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause*. 2018 Jul;25(7):837-847.
9. Labrie F, Archer DF, Koltun W et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause*. 2018 Nov;25(11):1339-1353.
10. Mitchell CM, Reed SD, Diem S et al. Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. *JAMA Intern Med*. 2018 May 1;178(5):681-690.
11. Chatsipiroios D, Schmidts-Winkler IM, König L et al. Topical treatment of vaginal dryness with a non-hormonal cream in women undergoing breast cancer treatment - An open prospective multicenter study. *PLoS One*. 2019 Jan 24;14(1):e0210967.
12. Jain AL, Jamy O, Mullins J et al. Usefulness of patient-reported outcomes to assess the effectiveness of topical hormonal therapy for gynecologic symptoms after antihormonal treatment for breast cancer. *Proc (Bayl Univ Med Cent)*. 2020 Apr 7;33(3):331-335.
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Guidelines Breast
Version 2023.1E

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FORSCHEN
LEHREN
HEILEN

Einschätzung der sexuellen Gesundheit¹

- Kurze Checkliste Sexueller Symptome für Frauen (BSSC-W)²
- Screening-Fragebogen zur Sexualfunktion insgesamt

1. Sind Sie zufrieden mit Ihrem Sexualleben? Ja – Nein

Wenn nein, dann beantworten Sie bitte die nächsten Fragen:

2. Seit wann/wie lange sind Sie mit Ihrem Sexualleben unzufrieden?

3a. Ihr Problem im Sexualleben ist: (eins oder mehrere markieren)

1. Problem mit weniger oder gar kein Interesse bzw. Lust	0
2. Problem mit reduzierter Empfindlichkeit / Sensibilität im Genitalbereich (Gefühl)	0
3. Problem mit verringerter vaginaler Lubrikation (Trockenheit der Scheide)	0
4. Problem, einen Orgasmus zu erreichen	0
5. Probleme mit Schmerzen beim Geschlechtsverkehr	0
6. Andere Probleme oder Sorgen

3b. Welche Probleme stören Sie am meisten? Bitte ankreuzen: 1 – 2 – 3 – 4 – 5 – 6

4. Wollen Sie über diese Probleme mit Ihrem Arzt/Ihrer Ärztin reden? Ja – Nein

- Sexual Complaints Screener For Women (SCS-W)^{3,4}
- FSFI-19, FSFI-6^{5,6}

General recommendations

1. Hatzichristou D, Rosen RC, Denogatis LR et al.: Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348

Brief Sexual Symptom Checklist (BSSC-W)

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Female Sexual Function Index (FSFI-19, FSFI-6):

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