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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 2015–2019:**
Albert / Bauerfeind / Blohmer/ Fersis / Gerber / Hanf / Huober/
Loibl / Maas / Scharl / Thill / Witzel
- **Version 2020:**
Rody/Witzel

Screened data bases:

Pubmed	2009 –2019
ASCO	2009 - 2019
Cochrane	2009 - 2019
Medline	2009 - 2019

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer			
	Oxford		
	LoE	GR	AGO
▪ Endocrine responsive disease (ER pos.)	1b	B	-
▪ Endocrine non-responsive disease (ER neg.)	2b	D	+/-
▪ Endocrine responsive disease (ER pos.): combined treatment TAM plus low-dose-HT	2b	B	+/-
▪ Tibolone	1b	A	-
▪ Topical vaginal application of			
▪ Estriol (E3 0.03 mg as treatment course*)	4	D	+/-
▪ Estradiol (E2) during AI therapy	4	C	-

* 4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week

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Endocrine responsive disease

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.

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. 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.
2. 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.

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. Mazzaello 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. doi: 10.1007/s10549-015-3434-z. Epub 2015 May 24.
7. Melisko ME, Goldman ME, Hwang J et al. (2017): 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*. 3(3):313-319.
8. 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



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Further Medical Approaches to Reduce Menopausal Symptoms I

Medical approaches:

- Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients
 - Venlafaxine
 - Desvenlafaxine
 - sertraline, escitalopram
- Gabapentin (patients using TAM)
- Pregabalin
- Clonidine (patients using TAM)
- Oxybutynin (2,5mg/5 mg)
- MPA (i.m. 500 mg single shot)
(most potent, but endocrine agent!)
- Vitamin E
- Omega 3 fatty acids
- Melatonin (improvement in sleep quality)
- Duloxetine (treating arthralgias while on AI)

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

1. 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.
2. 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).
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
4. 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.
5. 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.
6. Wiśniewska I, Jochymek B, Lenart-Lipińska M et al.: The pharmacological and hormonal therapy of hot flushes in breast cancer survivors. Breast Cancer. 2016 Mar;23(2):178-82.
7. 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.

8. 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, Shen Y, Cai Y, Zhang J.: Efficacy and Safety of Gabapentin and Pregabalin in Patients with Vasomotor Symptoms: a Systematic Review and Meta-Analysis. *Am J Obstet Gynecol*. 2019 Dec 20. pii: S0002-9378(19)32768-1. doi: 10.1016/j.ajog.2019.12.011. [Epub ahead of print] Review

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.

Clonidin

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 (Clonidin)

Oxybutynin

1. Roberto A. Leon-Ferre, Paul J. Novotny, Stephanie S. Faubion et al. A randomized, double-blind, placebo-controlled trial of oxybutynin for hot flashes : ACCRU study SC-1603. SABCS 2018, abstract GS6_2 (2019: nicht voll publiziert)

(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.



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CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

During anti-cancer treatment: Beware of drug interactions!

■ Soy-derived phytoestrogens – isoflavonoids*

Hot flush

Sleep disturbance

Topical vaginal application

■ Red Clover isoflavonoids*

Hot flush, sleep disturbance

■ Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d)
(reduces relapses, no effect on hot flashes)

■ Black Cohosh for hot flushes

Black cohosh + St. John's Wort

■ St. John's Wort

(pharmacokinetic interference with endocrine therapy,
cytotoxic drugs and tyrosin kinase inhibitors)

■ Ginseng root (Panax ginseng or P. quinquefolius)

■ Bromelain + Papain + Selenium + Lektin (for AI induced joint symptoms)

■ Homeopathic medicine to reduce hot flushes

Oxford		
LoE	GR	AGO
1b	B	-
1b	B	+/-
1b	B	+/-
1b	B	+/-
1b	B	+/-
2b	B	+/-
1b	B	+/-
1b	B	+/-
1b	B	+/-
1b	B	-
3b	B	+
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- derieived 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.

Sodium selenite, proteolytic plant enzymes (bromelaine 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		
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2020.1	General approaches:		
www.ago-online.de FORSCHEN LEHREN HEILEN			
	Oxford		
	LoE	GR	AGO
■ Physical exercise	1A	A	++
■ Mind body-medicine (yoga, hypnosis, education, counseling, mindfulness training)	1b	B	+
■ Cognitive behavioral therapy (CBT)	1a	A	++
■ (Electro) Acupuncture			
Aromatase-inhibitor treatment induced arthralgia	1b	B	+
Hot flushes	1a	B	+/-
Depression	2b	B	+/-
Anxiety, Sleep	3b	C	+/-

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. doi: 10.1136/bmjopen-2017-015860.

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 Database Syst Rev 2018, 1:Cd011292.

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


Cognitive behavioral therapy

1. Desautels C, Savard J, Ivers H et al.: Treatment of Depressive Symptoms in Patients with Breast Cancer: A Randomized Controlled Trial Comparing Cognitive Therapy and Bright Light Therapy. *Health Psychol*. 2017 Nov 27. doi: 10.1037/hea0000539. [Epub ahead of print]
2. Mann E: Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. *Lancet Oncol*. 2012 Mar;13(3):309-18.
3. Mewes JC, Steuten LM, Duijts SF et al.: Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients. *J Cancer Surviv*. 2015 Mar;9(1):126-35. doi: 10.1007/s11764-014-0396-9. Epub 2014 Sep 2.

4. van Driel CM, Stuursma A, Schroevers MJ et al. Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis. *BJOG*. 2019 Feb;126(3):330-339. doi: 10.1111/1471-0528.15153. Epub 2018 Mar 15.

Acupuncture

1. Befus D, Coeytaux RR, Goldstein KM et al. Management of Menopause Symptoms with Acupuncture: An Umbrella Systematic Review and Meta-Analysis. *J Altern Complement Med*. 2018 Apr;24(4):314-323. doi: 10.1089/acm.2016.0408. Epub 2018 Jan 3.
2. Chiu HY1, Shyu YK, Chang PC et al.: Effects of Acupuncture on Menopause-Related Symptoms in Breast Cancer Survivors: A Meta-analysis of Randomized Controlled Trials. *Cancer Nurs*. 2016 May-Jun;39(3):228-37.
3. Chen L, Lin CC, Huang TW et al.: Effect of acupuncture on aromatase inhibitor-induced arthralgia in patients with breast cancer: A meta-analysis of randomized controlled trials. *Breast*. 2017;33:132-8.
4. Chien TJ, Hsu CH, Liu CY et al.: Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis. *PLoS One*. 2017;12(8):e0180918.
5. Garland SN1, Xie SX, Li Q et al.: Comparative effectiveness of electro-acupuncture versus gabapentin for sleep disturbances in breast cancer survivors with hot flashes: a randomized trial. *Menopause*. 2017 May;24(5):517-523. doi: 10.1097/GME.0000000000000779.
6. Hershman DL, Unger JM, Greenlee H et al.: Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. *Jama* 2018, 320:167-76
7. Wang W, Liu Y, Sun S et al. Electroacupuncture for postmenopausal women with stress urinary incontinence: secondary analysis of a randomized controlled trial. *World J Urol*. 2018 Oct 13. doi: 10.1007/s00345-018-2521-2. [Epub ahead of print]

	Oxford		
	LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<p>Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)</p>		
<ul style="list-style-type: none"> Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information www.fertiprotekt.com) 			++
<ul style="list-style-type: none"> CT + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independent of hormone receptor status) 	1a	A	+
<ul style="list-style-type: none"> CHT + GnRHa (preservation of fertility) 	1b	A	+/-

Ovarian function protection

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Ovarieller Funktionserhalt – Synopsis der randomisierten Studien

	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. 4700mg	4080 vs. 4008 mg	n.r.	n.a.	5940 vs. 5940mg

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Assessment of Ovarian Reserve

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

Tests for fertility assessment

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

* Tests are suggested for women > 35y 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.


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FSH

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Contraceptive Options for Women after Diagnosis of Breast Cancer

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- **Barrier methods**
- **Sterilization (tubal ligation/salpingectomy/vasectomy)**
- **Non-hormonal intrauterine devices (IUDs)**
- **Levonorgestrel-releasing IUDs**
 - Removal in newly diagnosed patients
- **Timing methods**
- **Injectable progestin-only contraceptives**
- **Progestin-only oral contraceptives**
- **Combined oral contraceptives**
- **Emergency Contraception Options**
 - Copper intrauterine device (Cu-IUD)
 - Levonorgestrel, Ulipristal orally

Oxford		
LoE	GR	AGO
5	D	+
5	D	+
3b	D	+
2b	C	-
4	D	+/-
5	D	-
5	D	-
5	D	-
5	D	-
5	D	+
5	D	+

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Emergency Contraception - Options after Diagnosis of Breast Cancer

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Sexual Health			
	Oxford		
	LoE	GR	AGO
■ Use of patient-reported questionnaires	4	C	+
■ Assessment of sexual dysfunction	5	D	+
■ Vaginal dryness:			
Non-hormonal lubricants / moisturizers	1b	B	+
■ Fractionated microablative CO2-Laser/Vaginal Erbium:YAG-Laser	2a	B	+/-
■ DHEA local application	2b	B	+/-
■ Topical vaginal application of			
■ Estriol (E3 0.03 mg as treatment course*)	4	D	+/-
■ Estradiol (E2) during AI therapy	4	C	-
■ Psychoeducational support, group therapy, sexual counseling, marital counseling, psychotherapy	1b	B	+

* 4 weeks daily 1 x 1, followed by 8 weeks 3 x 1 per week

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Assessment of Sexual Health

■ **Sexual Complaints Screener (SCS) for women***
German Translation

Screening-Check-Fragebogen: Overall Sexual Function

1. Are you satisfied with your sexual life? yes, no; if no
2. How long have you been dissatisfied with your sexual life?
3. The problems with your sexual life are: (mark one or more):
 1. Problem with little or no interest in sex
 2. Problem with decreased genital sensation (feeling)
 3. Problem with decreased vaginal lubrication (dryness)
 4. Problem reaching orgasm
 5. Problem with pain during sex
 6. Other
4. Which problem is most bothersome? (circle) 1, 2, 3, 4, 5, 6.
5. Would you like to talk about it with your doctor?

* Hatzichristou D, Rosen RC, Denogatis LR, Low WY, Sadovsky R, Symonds T. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348

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