Vaginal Atrophy and Female Sexual Dysfunction Treatment Chart

During peri-menopause and menopause, vaginal atrophy and sexual dysfunction are often reported as problematic. Untreated vaginal atrophy can lead to painful sex and low desire. We recognize that sexual dysfunction can be caused by other causes, and a thorough evaluation needs to be done to determine if hormones or other therapies may be of benefit. Currently, there are not any FDA approved treatments for women for sexual dysfunction. Treating vaginal atrophy can include both hormone and hormone free treatment options. The chart lists active ingredients that can be used to treat vaginal atrophy and sexual dysfunction. Some information listed is anecdotal, however worthy of mention.

Testosterone, dehydroeipandrosterone and sildenafil have been studied in women for sexual dysfunction; however there are no products currently on the market for women. Often compounds for sexual dysfunction will contain several actives, designed to increase nitric oxide for vasodilation in genital tissue. Many over-the- counter products designed for women contain menthol, niacin or arginine. As compounds, many practitioners will add niacin or arginine to topical creams containing sildenafil and/or testosterone. This is a guide designed to deliver information to help with therapy decisions.

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Drug	Mechanism of Action	Dosing	Notes	References
Arginine HCl USP	Precursor for nitric oxide→ relax smooth muscles and circulation enhancement→ engorgement of genital tissue	Orally 2500 mg/day, Topically 3 – 20 % *anecdotal information	Must be used daily; oral use seen weeks for benefit; Oral dosage form - commercially available, study available. Topical use some positive feedback, however must be used daily at high dosing.	Ito TY, Polan ML, Whipple B, Trant AS. The enhancement of female sexual function with arginmax, a nutritional supplement, among women differing in menopausal status. *J Sex Marital Ther.* 2006 Oct-Dec;32(5):369-78 http://www.arginmax.com/couples-sexual-health-supplements-lf.php?gclid=CO_I-PPDtbACFVPftgodw2qx7w (last accessed 23 Oct 2012)
Menthol USP	Vasodilator; tingling cooling effect	Up to 0.025 % topical *anecdotal use 0.16%	May burn or cause genital irritation; do not apply to broken or irritated skin	No studies found Be careful on amount used to avoid irritation
Niacin (nicotinic acid)	Vasodilator	Up to 2 % topical		No studies found
Peppermint oil	High menthol content Cooling effect, tingling	0.1 mL/100 grams	The amount used should be small percent, and consider amount being applied.	No studies found
Vitamin E acetate	Anti-inflammatory, antioxidant, skin/wound healing	200 – 400 iu/day oral	No literature for monotherapy; could use 100 iu-400 iu intravaginal as a cream	No studies found
		1 iu (mg)/intra-vaginal dose	Combination therapy	Costantino D, Guaraldi C. Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial. *Eur Rev Med Pharmacol Sci.* 2008 Nov-Dec;12(6):411-6
Vitamin A palmitate	Increases function of immune local cells and integrity of vaginal epithelium	1 mg/intra-vaginal dose	Combination therapy	Costantino D, Guaraldi C. Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial. *Eur Rev Med Pharmacol Sci.* 2008 Nov-Dec;12(6):411-6
Sodium hyaluronate	Moisturizer; maintains water balance aiding in skin elasticity	5 mg intra-vaginally every other day x 2 weeks, then twice weekly	30 participants experienced reduced symptoms & increase incidence of superficial and intermediate cells after treatment for 90 days.	Karaosmanoglu O, Cogendez E, Sozen H, et al. Hyaluronic acid in the treatment of postmenopausal women with atrophic vaginitis. *Int J Gynaecol Obstet.* 2011 May;113(2):156-7. Epub 2011 Mar 21
		5mg per ovule (combination with vitamin A & E) QHS x 2 weeks, then every other day	130 women reported significant improvement in vaginal itching, burning, irritation and dyspareunia. Total 4 weeks	Costantino D, Guaraldi C. Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial. *Eur Rev Med Pharmacol Sci.* 2008 Nov-Dec;12(6):411-6

Estrogen	Acts locally to increase secretions, decrease vaginal pH and prevent urogenital infections; stimulates cell proliferation of vaginal mucosa and lower urinary tract	10µg and 25µg vaginal tablets	230 women included. Both doses provided relief (25µg showed greater benefit) of vaginal symptoms & increased vaginal and urethral maturation.	Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M. Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: A randomized controlled trial. *Obstet Gynecol.* 2008 Jan; 111(1):67-76.
		10µg 17β-estradiol vaginal tablet	309 women studied. Treatment effect on vaginal cytology and maturation seen after 2 weeks. Symptom relief apparent after 4 weeks.	Simon J, Nactigall L, Gut R, Lang E, Archer D, Utian W. Effective treatmetn of vaginal atrophy with an ultra-low-dose estradiol tablet. *Obstet Gynecol.* 2008 Nov; 112(5): 1053-60.
		12.5µg micronized estradiol vaginal tablet twice weekly for 12 weeks	In 8 breast cancer survivors, provided improvement in vaginal symptoms and sexual function with insignificant change in serum estrogen levels.	Biglia N, Peano E, Sgandurra P, Moggio G, Panuccio E, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: A preliminary study. *Gynecol Endocrinol.* 2010 June;26(6):404-412.
		1gm cream containing 0.625mg conjugated equine estrogens +/- 0.5gm 0.2% testosterone cream	75 postmenopausal women experienced significant benefit in urogenital and sexuality score and vaginal health and maturation indices after 12 weeks in both treatment groups.	Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparitive study of the effects of local estrogen with or without testosterone on vulvovaginal and sexual dysfunction in postmenopausal women.
Estriol (Estriol USP does not have an FDA approved indication)	Decreases vaginal pH → increases presence of vaginal lactobacillus thus prevention of urogenital infections; promotes cell proliferation of the vaginal mucosa	1mg vaginal ovule qd x 2 weeks, then 2 ovules once weekly for a total of 6 months	In 88 postmenopausal women, significant improvement in symptoms was seen.	Dessole S, Rubattu G, Ambrosini G, et al. Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women. *Menopause.* 2004 Jan-Feb;11(1):49-56
		1mg/day intravaginal x 21 days	In 31 postmenopausal women, all complaints improved and an increase in estrogenic level was observed.	Chuery AC, Speck NM, deMoura KF, Belfort PN, Sakano C, Ribalta JC. Efficacy of vaginal use of topical estriol in postmenopausal women with urogenital atrophy. *Clin Exp Obstet Gynecol.* 2011;38(2):143-5
		0.03mg and 0.2mg pessiaries daily x 20 days, then twice weekly for 9 weeks	438 total study subjects. Improvement comparable between doses in vaginal pH and atrophy symptoms. Greater improvement with 0.2mg dose in vaginal maturation index.	Grisser H, Skonietzke S, Fischer T, Fielder K, Suessking M. Low dose estriol pessaries for the treatment of vaginal atrophy: a double-blind placebo-controlled trial investigating the efficacy of pessaries containing 0.2 mg and 0.03 mg estriol. *Maturitas.* 2012 Apr;71(4):360-8. Epub 2012 Jan 28
		0.5mg/day vaginal cream daily x 3 weeks, then twice weekly through 4 months	In 27 early postmenopausal women, vaginal estriol improved vaginal symptoms sooner than HT alone; both evolved to show similar improvement at the end of the 4 month study.	Palacios S, Castelo-Branoc C, Cancelo MJ, et al. Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. *Maturitas.* 2005;50:98-104

Estriol continued	See above	0.25mg cream twice weekly x 12 weeks	In 10 breast cancer survivors, provided improvement in vaginal symptoms and sexual function with insignificant change in serum estrogen levels.	Biglia N, Peano E, Sgandurra P, Moggio G, Panuccio E, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: A preliminary study. *Gynecol Endocrinol.* 2010 June;26(6):404-412.
		1gm gel containing 50µg estriol daily x 3 weeks, then twice weekly up to 12 weeks	Study of 167 women. Low-dose estriol shown to be superior to placebo in improvement of vaginal dryness.	Cano A, Estévez J, Usandizaga R, Gallo JL, et al. The therapeutic effect of a new ultra low concentration estriol gel formulation (0.005% estriol vaginal gel) on symptoms and signs of postmenopausal vaginal atrophy: results from a pivotal phase III study. *Menopause* . 2012 Oct;19(10)1130-39
Progesterone	Precursor for estriol and testosterone; mood stabilizer	30mg intravaginal Oral HRT supplementation may be beneficial	Used in combination with estriol	No studies found for monotherapy
Estriol/ Progesterone (combination)	See estriol and progesterone above	1mg estriol + 30mg progesterone suppository daily x 2 weeks, then 3X/week through 6 months	19 women with atrophic vaginitis treated an observed improvements in vaginal dryness without endometrial hyperplasia	Chollet JA, Carter G, Meyn LA, Mermelstein F, Balk JL. Efficacy and safety of vaginal estriol and progesterone in postmenopausal women with atrophic vaginitis. *Menopause.* 2009 Sep-Oct;16(5):978-83
		50µg/day 17-β estradiol transdermal + 5mg/day oral medroxy-progesterone acetate plus 0.5mg/day estriol cream	In 27 early postmenopausal women, vaginal estriol improved vaginal symptoms sooner than HT alone; both evolved to show similar improvement at the end of the 4 month study.	Palacios S, Castelo-Branoc C, Cancelo MJ, et al. Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. *Maturitas.* 2005;50:98-104
Alprostadil (prostaglandin E_1)	↑ cAMP → smooth muscle relaxation & vasodilation; enhances nerve sensation	0.05, 0.1, and 0.2% cream applied to vaginal wall in office	Patients reported significant increases in amount of lubrication with higher doses and increased subjective arousal.	Islam A, Mitchel J, Rosen R, Phillips N, Ayers C, Ferguson D, Yeager J. Topical alprostadil in the treatment of female sexual arousal disorder: a pilot study. *J Marital Therapy.* 2001 Oct-Dec;27(5):531-40
		500, 1000, 1500mcg cream applied to vulvar area 5-30 min prior to anticipated sexual intercourse	94 premenopausal women with FSAD; changes indicate improvements in sexual activity and sexual distress levels, greatest benefits seen in 1000mcg dose.	Padma-Nathan H, Brown C, Fendl J, Salem S, Yeager J, Harninqr R. Efficacy and safety of topical alprostadil cream for the treatment of female sexual arousal disorder (FSAD): a double-blind, multicenter, randomized, and placebo-controlled clinical trial. *J Sex Marital Ther.* 2003 Oct-Dec;29(5):329-44
		100mcg or 400mcg solution applied to external genitalia in office	39 patients receiving 400mcg experienced significantly greater changes in genital warmth/tingling, level of sexual arousal, and sexual satisfaction.	Heiman J, Gittelman M, Costabile R, Guay A, Friedman A, Heard-Davison A, Peterson C, Dietrich J, Stephens D. Topical alprostadil (PGE_1) for the treatment of female sexual arousal disorder: In-clinic evaluation of safety and efficacy. *Journal of Psychosomatic Obstetrics & Gynecology* . 2006 Mar; 27(1): 31-41.
		500, 700, and 900mcg cream applied 5-30min prior to sexual intercourse	374 women with FSAD completed the study; treated patients oberved improved sexual arousal rates.	Liao Q, Zhang M, Geng L, Wang X, Song X, Xia P, Lu T, Lu M, Liu V. Efficacy and safety of alprostadil cream for treatment of female sexual arousal disorder: A double-blind, placebo-controlled study in Chinese population. *J Sex Med* . 2008; 5: 1923-1931.

Testosterone	Precursor for other sex hormones (DHT and estradiol)	300mcg patch twice weekly in naturally postmenopausal women on stable oral HRT	433 women included. Satisfying sexual activity seen at 4 weeks; improved desire and personal distress not seen until 8 weeks	Shifren J, Davis S, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. *Menopause.* 2006 Sep-Oct;13(5):770-9
		Dosing that is consistent with levels seen in younger patients with normal menses	Testosterone administered in physiological doses by non-oral route appears safe for up to 2 years when given with exogenous estrogens	Braunstein GD. Management of female sexual dysfunction in postmenopausal women by testosterone administration: safety issues and controversies. *J Sex Med.* 2007;4:859-66
		10 mg cream daily to thigh x 12 weeks	Study included 34 premenopausal women. Restored general well-being, and nearly half of women experienced a 50% improvement in sexual function score	Goldstat R, Griganti E, Tran J, Wolfe R, Davis S. Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause.* 2003 Sep-Oct;10(5):390-8
		2.2 mg/day alcoholic gel to upper arm	BLISS study, designed to evaluate long-term CV safety and risk of breast cancer. Currently enrolling and randomizing patients.	White WB, Grady D, Giudice LC, Berry SM, Zborowski J, Snabes MC. A cardiovascular safety study of LibiGel (testosterone gel) in postmenopausal women with elevated cardiovascular risk and hypoactive sexual desire disorder. *Am Heart.* 2012;163:27-32
		10 mg applied to thigh or abdomen	Controlled cross-over design of 131 postmenopausal cancer survivors. Estradiol-depleted patients did not see benefit in libido, pleasure, mood, or vitality in 4-weeks of treatment.	Barton DL, Wender DB, Sloan JA, Dalton RJ, Balcueva EP, Atherton PJ, Bernath AM Jr, DeKrey WL, Larson T, Bearden JD 3rd, Carpenter PC, Loprinzi CL. Randomized controlled trial to evaluate transdermal testosterone in female cancer survivors with decreased libido; North Central Cancer Treatment Group protocol N02C3. J Natl Cancer Inst. 2007 May 2;99(9):672-9
		Vaginal atrophy, 1 gram dose: 150 mcg (used testosterone propionate) OR 300 mcg (used testosterone micronized) cream; Avoid use on labia majora, clitoris	In 20 women currently on AI's, Improvement in severity of dyspareunia and vaginal dryness. No difference in symptom severity between the 150µg and 300µg doses given for 28 days.	Witherby S, JohnsonJ, Demers L, et alTopical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study Oncologist. 2011;16(4):424-31. Epub 2011 Mar 8
Dehydroepi-androsterone (DHEA)	Precursor for androgens and estrogens that promote collagen formation in the vaginal epithelium, lamina propria and muscularis (proposed MOA for improvement of vaginal atrophy)	3.25mg 6.5mg, 13mg intravaginal ovule QHS *consider oral BHRT dosing *consider clitoral cream	216 postmenopausal participants, marked improvements in sexual desire, arousal, orgasm, and pain during intercourse seen with 12 weeks of treatment	Labrie F, Archer D, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause.* 2009 Sep-Oct;16(5):923-31
			DHEA serum levels and metabolites measured; values remained within normal range for postmenopausal women	Labrie F, Archer D et al. Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. *Menopause.* 2009 Sep-Oct;16(5):897-906

Dehydroepi-androsterone (DHEA) continued	see above	15mg transmucosal daily	case report in female for libido with success	Dr. Johnathan Wright Nutrition & Healing Vol 15, Issue 10 December 2008
		4g 10% DHEA cream or gel applied to thighs, or two 50mg oral caps daily before breakfast	DHEA is transformed into active androgens and estrogens in peripheral intracrine tissues with minimal/no release of active steroids into circulation.	Labrie F, Bélanger A, et al. Bioavailability and metabolism of oral and percutaneous dihydroepiandrosterone in postmenopausal women. Journal of Steroid Biochemistry & Molecular Biology. 2007; 107: 57-69.
Sildenafil	Proposed mechanism in females: relaxation of clitoral and vaginal smooth muscle and vasodilation allowing for improved blood flow in the gentials	50mg 1 hour prior to planned sexual activity, no more than once daily x 3 months	Of 30 women treated, non-significant increase in subjective lubrication and clitoral sensation scores.	Kaplan S, Reis R, Kohn I, et al. Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. *Urology.* 1999 Mar;53(3):481-86
		25-100mg x 12 weeks	202 post-menopausal women; those without HSDD had significant benefit in arousal sensation, lubrication, and orgasm.	Berman JR, Berman LA, Toler SM, et al. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. *J Urol.* 2003 Dec;170(6 Pt 1):2333-8
		10-100 mg oral no > once daily x 12 weeks *anecdotal: Topical 0.5 - 3%	577 estrogenized and 204 estrogen-deficient women tolerated therapy, but did not perceive improvement in sexual response including vaginal lubrication and clitoral sensation.	Basson R, McInnes R, Smith MD, Hoggson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. *J Womens Health Gend Based Med.* 2002 May;11(4):367-77
Nifedipine	Vasodilation	0.2% topical		No studies found
Ergoloid mesylate	Proposed mechanism – vasodilation; Alpha receptor blocker, regulates smooth muscle responsiveness, may facilitate vasodilation in combination	0.05% topical	36 men studied; Significantly increased penile arterial flow and improved erectile dysfunction without producing clinically significant side effects. More effective in psychogenic than organic vascular impotence.	Gomaa A. Shalaby M, Osman M, et al. Topical treatment of erectile dysfunction;randomized double-blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate *International Journal Pharmaceutical Compounding Vol.6 No 4 July/Aug 2002*
Isosorbide dinitrate	Converts to nitric oxide → vasodilation	0.25 % topical	See above	See ergoloid mesylate reference
Aminophylline (releases theophylline)	Non selective phosphodiesterase inhibitor, ↑ cAMp → smooth muscle relaxation	3% (study); May need higher doses as anecdotally seen topical dosing 3 – 10 %	See ergoloid mesylate note	See ergoloid mesylate reference

Naltrexone	Counteracts the effects of endogenous opiates thought to contribute to sexual dysfunction by inhibiting gonadotropins	25 mg oral daily for 3 days	Study with 20 male participants; number of orgasms, intensity of arousal and orgasm were greater under treatment conditions.	Sathe RS, Komisaruk BR, Ladas AK, Godbole SV. Naltrexone-induced augmentation of sexual response in men. *Arch Med Res.* 2001 May-Jun;32(3):221-6
		25 mg oral once daily x 4 weeks, then bid x 4 weeks. Topical dose of 0.817% was shared by member pharmacist.	9 men treated observed a rise in spontaneous morning erections; 6 of 9 reported subjective improvement, 3 of which regained full erectile function.	Brennemann W, Stitz B, Van Ahlen H, Brensing KA, Klingmuller D. Treatment of idiopathic erectile dysfunction in men with the opiate antagonist naltrexone—a double-blind study. *J Androl.* 1993 Nov-Dec;14(6):407-10
Oxytocin	Enhances sexual arousal	Information below is anecdotal* Nasal spray 8-40 IU, Vaginal/clitoral cream 10-40 u/mL. Troches or SL drops ranges 5-100 u/dose: 5 -20 units every morning to increase happiness, social connectedness. For low oxytocin levels and for better orgasm, consider 50-100 units 1 hour prior to sex.	32 year old male patient experienced improvements in libido, sexual arousal, erectile function, and satisfaction with orgasm. Intranasl dose of 20 units BID, targeting social anxiety and avoidance, led to increase of spontaneous affection towards wife, & increasing sexual intimacy.	MacDonald K, Feifel D. Dramatic improvement in sexual function induced by intranasal oxytocin. *J Sex Med.* 2012 Mar;9:1407-10
			Intranasal administration leads to marked increase in plasma levels, and study suggests altered perception of arousal.	Burri A, Heinriches M, Schedlowski M, Kruger TH. The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. *Psychoneuroendocrino.* 2008 Jun;33(5):591-600
Cyproheptadine	5HT-2 Antagonist may reverse the inhibiting effect of anti-depressants on orgasm.	Consider a clitoral cream(1 - 4 mg) to prevent oral side effects.	4-12 mg orally 1-2 hr prior to sexual activity or up to 16 mg daily in divided doses. In 7 males with SRI-induced sexual dysfunction;	Aizenberg D, Zemishlany Z, Weizman A. Cyproheptadine treatment of sexual dysfunction induced by serotonin reuptake inhibitors. *Clin Neuropharmacol.* 1995;18(4):320-24