Female Sexuality:
All you ever dreamed of knowing ..
Sex in women
Warning: The pictures that will follow are only for not too sensitive persons!
Difficulties in attracting a partner:
Lack of pheromones?
Pheromones
Biology & Chemistry of Pheromones
Pheromone

- comes from the Greek words *pherin*, to transfer, & *hormon*, to excite.
- similar to hormones but instead of working within the body, they work between bodies.
Pheromone

=> detected through an "alternative scent" organ in your nose called the vomeronasal organ, or the VNO.3 Up until about 15 years ago, the VNO was assumed to be vestigial - an organ leftover from primitive times that's no longer needed, and no longer in use. But in 1994, physiologists at the University of Utah examined 400 human subjects and found that they all had functioning vomeronasal organs …which were actively sending pheromonal messages not to the cerebral cortex…but to the limbic system.4
Hold it right there, young lady! Before you go out, you take off some of that makeup and wash off that gallon of pheromones!
SUBJECTS: 12 women who wore armpit pads for 24 h/day => restricted from eating certain foods & from using deodorant or hormonal contraceptive => odour samples => presented to 42 men, who sniffed them and assessed the attractiveness of the scent.

RESULTS:
• "Axillary odour from women in the follicular phase was rated= the most attractive & least intense," the study's leader Dr Jan Havlicek, from Charles University in Prague, Czech Republic, said.

CCL: body odour => used by men as a cue to the fertile period in current or prospective sexual partners," he added.

• Men said the women's odour was most intense during menstruation
• A woman's body odour can help her attract men when she is at her most fertile and repel them when she is not, scientists have said.
• According to a report in the, when a woman is at the most fertile part of the menstrual cycle => her armpit odour is at its mildest.
• But when she is having a period, and not ready for pregnancy => the smell changes to an acute, repellent odour.

Too much pheromones secreted in the armpit?

Follicular phase: less scent, more attractive
A previous study by the same team suggested that
SUBJECTS: 48 men => assess how dominant they felt => wore cotton
pads in their armpits for 24 h => presented to 65 women

RESULTS:
• Women who were ovulating rated the "dominant" men as sexiest
• No similar pattern among women at other stages of their menstrual
cycle
CCL: women subconsciously prefer the aroma of dominant men when
they are at the most fertile stage of the menstrual cycle

...
Sniffling male pheromones => increased energy, cortisol & sexual arousal in Women...

STUDY: published in the Journal of Neuroscience by researchers from the University of California at Berkeley => men emit pheromones - chemical compounds - in their sweat that affect the physiology of women.

SUBJECTS: 48 undergraduate women =>

TREATMENT: took 20 sniffs from containers of androstadienone, a main component found in male sweat, auxiliary hair, blood & semen secretions (vs sniffing of a controlled odor)

After testing the levels of cortisol, an adrenal hormone =>

- heightened energy
- increased blood pressure that remained at high levels for over an hour
- Higher cortisol
- a rise in heart rate
- sexual arousal
Red meat consumption => reduces body odor attractiveness

SUBJECT: 17 men = odor donors => "meat" or "nonmeat" diet for 2 weeks + axillary pads to collect body odor during the final 24 h of the diet.

=> Fresh odor samples were assessed for their pleasantness, attractiveness, masculinity, and intensity by 30 women not using hormonal contraceptives => repeated the opposite diet

RESULTS: the odor of donors when on the nonmeat diet => significantly more attractive, more pleasant, & less intense.

CCL: red meat consumption => negative impact on perceived body odor hedonicity.

DHEA-dependent
High DHEAs in infants with pubic hair

- +130% higher serum DHEA-S (17.5 vs. 7.6 µg/dl [476 vs. 207 nmol/l]; p = 0.067),
- 6 of 12 => levels >15 µg/dl (408 nmol/l) vs. one of 12 controls.
- Low serum testosterone levels (<10 ng/dl [<350 pmol/l]) in nearly all infants with pubic hair.

Significant beneficial effects of DHEA on sebum production

**French study**  
DHEâge (men & women > 60 yrs)  
Increase in sebum production (in %) after 1 year of DHEA

- + 66 % Compared to placebo  
- n= 140 + DHEA  
- n= 140 placebo

**Canadian Study**  
(women of 60 - 70 yrs)  
+ 73 % Compared to the initial production

- n= 15

P < 0.01

Un an de traitement à la DHEA par voie orale (étude française) ou par voie transdermale augmente la production de sébum considérablement, un effet anrogène typique. L’étude française a montré surtout une amélioration significative chez les femmes au-dessus de 70 ans qui avaient une peau qui sécrétait peu de sébum (p = 0.0001 avec une augmentation de 8.7 taches de sébum sur le strip à 52.4 (moyenne globale chez les traités: 101). Les femmes en-dessous de 70 ans étaient proches du significatif (0.07), ainsi que les hommes de moins de 70 ans (p= 0.11). L’étude canadienne a montré que l’effet sur le sébum disparaissait trois mois après traitement.


DHEA

- ↑ production of pheromones (through ↑ sebum)
- ↑ libido (mainly in women)
MSH Effects

Darkening of the armpits
Melanotan II

=> stronger scent or odor
Testo & alpha-MSH => synergistic effect on sebum secretion & on dermal & preputial gland lipogenesis

• SUBJECTS: hypophysectomized rats.
• RESULTS: Hypophysectomy reduced sebum secretion, sebaceous and preputial gland size, and dermal and preputial gland lipogenesis. The greatest effects were seen on the biosynthesis of wax esters and squalene. Testosterone propionate (TP) increased sebum secretion, sebaceous gland volume and preputial gland weight and lipogenic activity, but had no significant effect on the pattern of lipid labelling. alpha-MSH had no effect on sebaceous or preputial gland size, but increased sebum secretion and dermal lipogenesis, especially wax ester biosynthesis. When given together TP & alpha-MSH => synergistic effect on sebum secretion and on dermal and preputial gland lipogenesis, and the pattern of lipid labelling was shifted towards normal.
• TP and alpha-MSH => synergism in increasing preputial gland weight, but together they had no greater effect on sebaceous gland volume than that achieved with TP alone. These results suggest that TP and alpha-MSH have different actions on the sebaceous glands with alpha-MSH acting predominantly on lipogenesis and TP on cellular proliferation and turnover leading to an increase in gland size. Preputial glands differ from cutaneous sebaceous glands in their response to alpha-MSH and androgen which could be a reflection of their more specialized function.

TREATMENT doses for pheromones in women

- **DHEA** 5 to 30 mg/day
- Transdermal **Testosterone gel** 0.5%: ½ to 1 g/day (2.5 to 5 mg/day) TESTO IN HAIR
- !!!! Always testosterone in association with estradiol/progesterone (protective against virilization by androgens)
- **Melanotan II** 3x 0.3 mg/week

**Eroscent** (Smart 10 ml 145€)
Le coup de foudre :
« Ton œstradiol titille ma testostérone. »
References:


- Also called Jacobson’s organ, named after the Danish scientist who discovered a similar scent-detecting organ in the palate of the snake nearly 200 years ago.

Sexual arousal!
How to improve sexual arousal in women & orgasm
With hormone therapies?
Sexual arousal

Major hormones
• Testosterone
• Estradiol
• MSH
• Oxytocin
Oophorectomized women => more likely worsening of sexual fn after hysterectomy

SUBJECTS: Hysterectomized women
TREATMENT:
RESULTS: Women after bilateral oophorectomy (vs women who retain their ovaries)
• more likely to report a worsening of sexual function after hysterectomy, esp. adverse changes in libido & orgasmic response
• more likely to experience decreased positive psychological well-being.
CCL: important role for androgens in female sexual function & psychological well-being

Shifren JL. Androgen deficiency in the oophorectomized woman. Fertil Steril. 2002 Apr;77 Suppl 4:S60-2. Massachusetts General Hospital, Vincent Obstetrics and Gynecology Service, Boston, Massachusetts 02114, USA
Estradiol → increases Libido

Figure: many women complaining of sexual dysfunctions & estrogen deficiency are successfully treated w/ estradiol trans-dermal patch alone.

Oophorectomized women: estrogens are of little value in treating these specific sexual dysfunctions

SUBJECTS: Hysterectomized women
Group A (n = 33): oophorectomized, untreated (no estrogens)
Group B (n = 33): oophorectomized + estrogen replacement therapy (ERT)
Group C (n = 35): ovaries preserved and not receiving ERT

RESULTS: Oophorectomized women (+ or not estrogens)
• sexual life was impaired as compared to those with intact ovaries
• complained about less pleasure from coitus,
• impaired libido and lubrication.

Regardless of whether estrogens were administered or not a similar pattern was found, indicating that estrogens are of little value in treating these specific sexual dysfunctions

Women + Sexual Dysfunction => ↓ Androgen levels

**STUDY**: retrospective, observational assessment

**SUBJECTS**: 250 female patients + sexual dysfunction

**TREATMENT**: 

**RESULTS**: women + sexual dysfunction: in general,

- young,
- healthy, free of vascular risk factors;
- complained of combination of decreased desire, arousal, & orgasm;
- Sign. ↓ serum androgen levels

Talakoub L, Munarriz R, Hoag L, Gioia M, Flaherty E, Goldstein I. Epidemiological characteristics of 250 women with sexual dysfunction who presented for initial evaluation. J Sex Marital Ther. 2002;28 Suppl 1:217-24. Center for Sexual Medicine, Department of Urology, Boston University School of Medicine, Boston, Massachusetts, USA.
Androgen = critical for optimal sexuality

SUBJECTS: women + total abdominal hysterectomy + bilateral salpingo-oophorectomy approx. 4 years ago for benign disease. =>

TREATMENT:
• 1st group + IM estrogen-androgen 1x/ month (E-A)
• 2nd group => estrogen alone (E)
• 3rd group of women => untreated (uN)

RESULTS: Women + both sex steroids reported higher rates of
• sexual desire \( p < 0.01 \)
• sexual arousal \( p < 0.01 \)
• numbers of fantasies \( p < 0.01 \) than those who were either given E or who were untreated.
• changes in these sexual behaviors covaried with serum testosterone but not with plasma estradiol levels during the treatment month
• higher rates of coitus & orgasm in the E-A group during the first two postinjection weeks \( p < 0.01 \) coincident with their higher testosterone levels

CCl: androgen = critical for the maintenance of optimal levels of sexual functioning in postmenopausal women.

SUBJECTS: 53 postmenopausal women
TREATMENT: as a complement to their already on-going HRT =>10mg of a testosterone gel (Testogel, Besins-Iscovesco) or placebo => 3 + 3 months in a double blind, randomized, crossover
RESULTS: 10 mg transdermal testosterone (vs placebo)
• Sign. improved scores of
  – "frequency of sexual activity, orgasm and intercourse",
  – "sexual arousal, fantasies and enjoyment",
  – “satisfaction with orgasms",
  – "interest in sex"
• Testosterone levels increased more than 10-fold during treatment
• DHT-levels more than doubled
• Estrogen levels were not affected during the addition of testosterone.

No increased libido with transdermal testosterone in estrogen-deprived women

- STUDY: phase III randomized, placebo-controlled crossover clinical trial, we evaluated whether transdermal testosterone would increase sexual desire in Postmenopausal women with a history of cancer and no current evidence of disease were eligible if they reported a decrease in sexual desire and had a sexual partner. Eligible women were randomly assigned to receive in Vanicream for a testosterone dose of 10 mg daily or placebo Vanicream for 4 weeks and were then crossed over to the opposite treatment for an additional 4 weeks. The primary endpoint was sexual desire or libido, as measured using the desire subscales of the Changes in Sexual Functioning Questionnaire, as assessed at baseline and at the end of 4 and 8 weeks of treatment. Serum levels of bioavailable testosterone were measured at the same times. All statistical tests were two-sided. RESULTS: We enrolled 150 women. female cancer survivors => 2% testosterone results: Women who were on active testosterone cream had higher serum levels of bioavailable testosterone than women on placebo (mean change from baseline, testosterone versus placebo, week 4. 11.57% versus 0%, difference = 11.57%, 95% confidence interval [CI] = 8.49% to 14.65%; week 8, 10.21% versus 0.28%, difference = 9.92%, 95% CI = 5.42% to 14.42%; P<.001 for all).

CONCLUSION: Increased testosterone level did not translate into improved libido, possibly because women on this study were estrogen depleted.

Part 2 of Phase IIa trials involving post-menopausal women was presented at the International Society for the Study of Women's Sexual Health (ISSWSH) 2007 Annual Meeting.
Sexual arousal

DHEA works too
Figure: Significative effects of a 50mg/d DHEA treatment during 4 months in 24 women w/ adrenal insufficiency in a randomised placebo controlled double blinded study. Only the frequency of sexual thoughts or phantasies improved significantly after one month of treatment, more time was needed for improvement of other sexual parameters.

DHEA works

**SUBJECTS:** patients + androgen insufficiency + sexual dysfunction

**TREATMENT:** DHEA

**RESULTS:** DHEA therapy =>
- a sign. decrease in sexual distress
- a sign. increase in sexual function in the domains of desire, arousal, lubrication, satisfaction, & orgasm
- normalization to values within the physiologic range in the following androgens measured:
  - total testosterone,
  - free or bioavailable testosterone,
  - DHEA, DHEA-S, androstenedione.

**SIDE EFFECTS:**
- increased facial hair (11%), weight gain (7%),
- acne (5%), and skin rash (1%),
- temporary breast tenderness (1%),
- loss of head hair (1%)

**CCL:** androgen replacement therapy with DHEA = safe & effective treatment for androgen insufficiency and female sexual dysfunction.

Melanotan I: Afamelanotide

- Molecular Formula: $C_{78}H_{111}N_{21}O_{19}$
- Molecular Weight: 1646.85

Melanotan II:

- Molecular Formula: $C_{50}H_{69}N_{15}O_{9}$
- Molecular Weight: 1024.18

Bremelanotide:

- Molecular Formula: $C_{50}H_{69}N_{14}O_{10}$
- Molecular Weight: 1025.2

Lacks the C-terminal amide function.
Montreal lab of Jim Pfaus, world’s preeminent expert on bremelanotide.

A 50-year-old neuroscientist, Pfaus was in the last stages of preclinical trials aimed at getting FDA approval for bremelanotide. Originally developed as a self-tanning agent, the drug had been repurposed when male study subjects reported a surprising side effect: erections.

Pfaus showed me stunning testimonials from human test subjects. The drug worked equally well on women, who chronicled “an intense arousal” that lasted from six to 72 hours.

“I was focused on sex,” said one of the women.
TREATMENT doses for sexual arousal in women

- **Transdermal Testosterone gel** 0.5%: ½ to 1 g/day (2.5 to 5 mg/day)

- Sometimes in resistant situations:
  - **DHT 2.5 % (Andractim®) cream**, locally on clitoris

- **Bremelanotide**
- **Melanotan II** « X 0.3 mg/week
- **DHEA** 25 to 50 mg/day
- **Oxytocin** 5 to 2x 10 IU/day (sublingual)

!!!! Always testosterone in association with estradiol/progesterone (protective against virilization by androgens)
Ultimate sexual arousal
Sexual sensitivity!
Sexual sensitivity

2 major hormones

- Dihydrotestosterone
- Oxytocin
Androgen target tissues => ↑androgen conc. & ↑5-alpha-reductase activity;
Androgen conc. in genit. target tissues => similar in both sexes

SUBJECTS: women aged 16-87 yr. => labia majora, clitoris, pubic skin, thigh skin, striated muscle

RESULTS: In women: androgen tissue concentrations
- lower than in men, but in androgen target tissues such as the clitoris or labia majora, concentrations were little lower than in scrotal skin
- highest in specific androgen target tissues (labia majora, clitoris)
- lowest in thigh skin & striated muscle.
- The ratios of the 5 alpha-saturated metabolites (DHT + Adiol) to T or to T + Adion, resp. parallel total androgen concentrations
- the Adiol to DHT ratio, a parameter of 3 alpha-reductase activity,
- highest in striated muscle & thigh skin
- lowest in androgen target tissues (labia majora and clitoris).

CCL: in both men & women::
androgen target tissues => ↑androgen conc. & ↑5alpha-reductase activity;
androgen conc. in genital target tissues are similar in both sexes

Cyproterone acetate (without oestrogen) => ↓ Sexual responsiveness

SUBJECTS: 46 virilized women

TREATMENT: cyproterone acetate (androgen, androgen receptor blocker)

RESULTS: intensive cyproterone acetate medication of several months' duration without concurrent oestrogen. => depressed sexual tonus.

Androgens, not conjugated estrogens => play a pivotal role in sexual drive & enjoyment of women

**SUBJECTs:** 20 postmenopausal women dissatisfied w/ estrogen or estrogen-P

**STUDY:** Double-blind, randomized trial with hormone therapy for 8 weeks after a single-blind, placebo, lead-in period

**Treatment:** Oral conj. estrogens or conj. estrogens + androgen for 8 wks

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Placebo</th>
<th>Estrogen (progestin) therapy</th>
<th>Estrogen (progestin) - androgen therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual sensation &amp; desire</td>
<td>-</td>
<td>-</td>
<td>↑ after 4 &amp; 8 weeks</td>
</tr>
<tr>
<td>Serum estrogens (E1 &amp; E2)</td>
<td>-</td>
<td>↑↑</td>
<td>↑ sign. (↓ vs estrogen ther.)</td>
</tr>
<tr>
<td>SHBG</td>
<td>-</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Serum Free androgens</td>
<td>-</td>
<td>↓</td>
<td>↑</td>
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Sublingual testosterone
⇒ time lag before genital arousal in women

Sublingual intake of testosterone
⇒ Within 15’: sharp increase in plasma testosterone levels
  ⇒ Within 90’: decline back to baseline values.
⇒ 3 to 4(1/2) hours after reaching peak testosterone level ⇒
  statistically sign. ↑ in genital responsiveness (P = .04)
⇒ On the day of testosterone treatment: strong &
  statistically sign. association between the ↑ in genital
  arousal & subjective reports of "genital sensations" (P = .02) & "sexual lust" (P = .01) after 4(1/2) hours.

CONCLUSIONS:
⇒ There is a time lag in the effect of sublingually
  administered testosterone on genital arousal in women.
⇒ ↑ vaginal arousal ⇒ ↑ genital sensations & sexual lust

Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R. Time course of
effects of testosterone administration on sexual arousal in women. Arch Gen Psychiatry. 2000
Feb;57(2):149-53; discussion 155-6. Department of Psychonomics, Utrecht University, The
Clitoris
Clitoris

Labios menores
Labios mayores afastados
Uretra
Vagina

Clitoral hood
(retracted to uncover the glans)

Glans clitoris

Labia majora
Labia minora
The clitoral index (CI)

\[ \text{CI} = \text{product of the sagittal & transverse diameters of the glans (mm}^2) \]

- 95% (of 249 normal women) \( \Rightarrow \) CI < 35 mm\(^2\).

- Clitoromegaly when CI > 35 mm\(^2\)

Different types of clitoris

Higher androgen levels

Emergent
Pearl
Flat

Lower androgen levels

Burried
Split

The clitoral index (CI)

- CI = the product of the sagittal & transverse diameters of the glans; clitoromegaly (CI > 35 mm²)

SUBJECTS: 85 patients + clitoromegaly + at least 1 other clinical sign of excess adrogenic stimulation

RESULTS:
- 62% (53/85) => abnormally ↑ values for either or both total serum testosterone and 17-ketosteroid levels

Clitoris => predomination of DHT
Uterus, brain, pituitary gland => testosterone

SUBJECTS: 9 ovariectomized adult rhesus monkeys
TREATMENT: injected with 5.5 mCi [3H] testosterone => 30 min later, samples of 14 brain areas, pituitary gland, & peripheral tissues were removed

RESULTS:
• In nuclei from the clitoris => [3H] dihydrotestosterone was the major form of radioactivity
• in nuclei in all other brain samples & in the pituitary gland & uterus, [3H] testosterone predominated

Case Report: Woman with life-long absence of sexual drive; DHT => ↑ sex drive & enjoyment

**Case:** Woman

- Life-long absence of sexual drive
- Not responded to sex therapy or cognitive-behaviour psychotherapy undertaken at other clinics

**Observations:** Patient

- poorly developed external genitalia.
- Only lab abnormality = reduced 5-dihydrotestosterone

**Treatment:** Dihydrotestosterone gel on vulva

⇒ generated sexual drive &
⇒ her ability to become sexually aroused.

DHEA => \(\uparrow\) Clitoris size

SUBJECTS:
- 11 normal subjects (group 1)
- 18 hirsute patients with no clitoromegaly (group 2)
- 13 hirsute patients with clitoromegaly (group 3)
- 8 patients with clitoromegaly but no hirsutism (group 4).

RESULTS:
- Clitoromegaly without hirsutism is asso. => \(\uparrow\) serum DHEA & delta 4A
- Hirsutism without clitoromegaly is asso. => \(\uparrow\) serum T, DHT, & delta 4A but normal DHEA levels
- The clitoral index correlated \((P < 0.01)\) with DHEA levels in group 3 (hirsute patients with clitoromegaly)

Masturbation
Serum testosterone values correlated significantly only with masturbation.

SUBJECTS: 48 women with well-defined hypothalamo-pituitary disorders.

RESULTS: Two of the three women who did not report sexual problems had never had intercourse.

- only 7 women had hyperprolactinemia
- 79.2% (38/48) of the women => lack of or a considerable decrease in sexual desire
- 64.6% (31) Problems with lubrication
- 68.7% (33) Problems with orgasm.
- Serum testosterone values correlated sign. only with masturbation.

Hulter B, Lundberg PO. Sexual function in women with hypothalamo-pituitary disorders. Arch Sex Behav. 1994 Apr;23(2):171-83. Department of Neurology, Akademiska sjukhuset, Uppsala, Sweden. The extent to which hypothalamo-pituitary disorders in women affect sexual desire and sexual functions was investigated.
SUBJECTS: 26 postmenopausal women with sexual arousal disorder => questionnaires after taking either the drug or a dummy pill

RESULTS: Women on bremelanotide (vs placebo)
- 73% of the bremelanotide => feeling genitally aroused (vs with 23% + placebo)
- 43% => augmented their sexual desire (vs only 19% + placebo)
- Slightly more likely to have sex with their partners during the course of the trial vs those in the control group, although who initiated the romps was not specified

CCL: Bremelanotide may well have some mild aphrodisiacal properties.
Doses for sexual sensitivity in women

- Transdermal **Testosterone gel** 0.5%: ½ to 1 g/day (2.5 to 5 mg/day)

- Sometimes in resistant situations:
  Testosterone enanthate injections 50 mg/month

- **DHEA** 25 to 50 mg/day

!!!! Always in association with estradiol/progesterone (protective against virilization by androgens)

- **Melanotan II or bremelanotide** 3x 0.03 to 0.05 ml (0.3 to 0.5 mg)/week
Coitus!
Estradiol → coitus (women)  

Figure: estradiol (valeriate 10 mg) IM inj. 1x/ month ↑ the frequency of coitus & orgasm in oophorectomized women (total abd. hysterectomy & bilateral salpingo-oophorectomy approx. 4 yrs ago) esp. in the postinj. weeks (Schiavi BB et al. Psychosomatic Medicine 1987, 49: 397-409)
Estradiol & testosterone → orgasm (women)

Figure: estradiol (valeriate 10 mg) & combined testosterone (enanthate 150 mg) – estradiol (dienanthate 7.5 mg, benzoate 1 mg) IM inj. 1x/month ↑ the frequency of coitus & orgasm in oophorectomized women (total abd. hysterectomy & bilateral salpingooophorectomy approx. 4 yrs ago) esp. in the postinj. weeks (Schiavi BB et al. Psychosomatic Medicine 1987, 49: 397-409)
For intercourse

Women need to have reactive Adrenals

(Cortisol, DHEA, ..)
The relationship between age at first sexual intercourse & salivary cortisol stress reactivity (to the Trier Social Stress Test; TSST; consisting of public speaking and mental arithmetic) => healthy subjects (43 females & 36 males; ages 19-38).

Women => reporting earlier first intercourse had less intense cortisol increases in response to the stressor (a non-significant trend was observed for males), and faster recovery from the stressor.

Results were not confounded by age, oral contraceptive use, depression scores, smoking status, or body mass index.

CCL: earlier first intercourse is associated with less reactivity to and faster recovery from stress as indexed by this endocrine measure.

Brody S. Age at first intercourse is inversely related to female cortisol stress reactivity. Psychoneuroendocrinology. 2002 Nov;27(8):933-43. Center for Psychobiological and Psychosomatic Research, University of Trier, Karl-Marx Strasse 94, 54290, Trier, Germany. stuartbrody@hotmail.com
serum DHEAS => ↓ sexual fn

SUBJECTS: Women in the Penn Ovarian Aging Study were assessed at yearly intervals for 3 years.

TREATMENT:

RESULTS: sexual dysfunction ↑ with advanced menopausal status.

- postmenopausal women => 2.3 x as likely to experience sexual dysfunction vs premenopausal women (odds ratio 2.3, 95% [CI] 1.3-4.1).
- ↓ serum DHEAS => ↓ sexual fn (odds ratio 1.59, 95% CI 1.19-2.14).

Additional risk factors associated with sexual dysfunction:

- absence of a sexual partner (11.2, 95% CI 6.9-18.1)
- ↑ anxiety (3.8, 95% CI 1.6-9.2),
- children < age of 18 living at home (1.6, 95% CI 1.1-5.5)
- Lubrication, orgasm, & pain = spec. aspects of sexuality negatively affected by menopause.

Melanotan II => ↑ proceptive behaviors in female rats if progesterone is present

SUBJECTS: ovariectomized rats => 7+ subcut. estradiol benzoate (EB) + progesterone (P) (n=7); 7 + EB alone => appetitive & consummatory aspects of female sexual behavior sexual, incl. proceptivity (solicitations, hops & darts, ear wiggling, pacing) & receptivity (lordosis) => MT-II (1 & 3 mg/kg) or saline was inj. IV 10’ before each 30’ mating test.

RESULTS: In females
- with EB+P => both doses of MT-II => ↑ number of hops & darts & ear wiggling sign., but did not alter pacing or lordosis.
- With EB alone => no effect of MT-II on any of the parameters measured.

CCL: Progesterone interacts with MT-II to ↑ proceptive behaviors.
Because hops and darts = essentially solicitations, made in close proximity to the male, that indicate a desire on the part of females to receive mounts and intromissions, these data suggest that activation of melanocortin receptors may represent a promising mode of action for the treatment of women with hypoactive sexual desire.

Melanotan II: structure
Studies in rodents demonstrated that the drug not only gave male rats spontaneous erections, but also fomented sexual excitement in female rats, prompting them to wiggle their ears, hop excitedly, rub noses with males and otherwise display unmistakable hallmarks of rodent arousal.

Importantly, the females responded to the drug only under laboratory conditions where they could maintain a sense of control over the mating game. Take away the female's opportunity to escape or proceed at her preferred pace, and no amount of bremelanotide would get those ears to wiggle. In other words, Annette M. Shadiack, director of biological research of Palatin, said, "this doesn't look like a potential date-rape drug."
Women overdosed in sex hormones & Melanotan II
Dyspareunia
(painful coitus!)
Painful intercourse (dyspareunia)

4 major hormones
- Estradiol
- Progesterone
- Testosterone
- Cortisol
Orgasm!
Sexual arousal

4 major hormones
- Oxytocin
- MSH-derived melanotan II)
- Testosterone
- Estradiol
↑ serum oxytocin => ↑ Subj. orgasm intensity in multiorgasmic women
↑ serum oxytocin => ↑ anal contractions in men & women

SUBJECTS: 13 women & 10 men => each subject => 2 or more tests of self-stimulation to 5 min beyond orgasm.

REPORT:
• In both men & women => very ↑ positive assoc. between the % change in serum oxytocin from baseline to orgasm & systolic BP; oxytocin & anal electromyography (EMG), intensity prior to & during orgasm; anal photoplethysmography & EMG.
• ↑ number of anal contractions => ↑ duration of orgasm (highly correl.)
• 2 patterns of orgasm dep. on the presence or absence of a quiescent period between orgasmic contractions.
• EMG & APG amplitudes => correlated with the pattern of orgasm.
• Subjective orgasm intensity => sign. correl. w/ ↑ serum oxytocin in multiorgasmic women only

CASE: 26-year old woman, 17 months after the birth of her second child for some temporary help with the breast feeding of her nephew. => A progestogen only pill (levonorgestrel 30 µg) had been used since 15 months.

TREATMENT: synthetic oxytocin spray (Syntocinon; Sandoz) => on day 17 of her irregular cycle =>

=> About 2 h after the use of 2 activations (8 IU) of oxytocin, =>
• copious vaginal transudate trickling down her leg
• Intense sexual desire,
• cervix had opened slightly.
• initiated sex with her partner
• intensified uterine & vaginal contractions at orgasm
• heightened subjective pleasure.

Oxytocin was repeated on day 19 with similar effects lasting again for 3 hours after their onset. 7 to 10 days later she ceased taking levonorgestrel & restarted barrier contraception. 2 weeks later she readministered the spray but no sexual responses occurred.

• She also described feelings of mild arousal with breast feeding her children, an experience common among other women.

Estradiol $\rightarrow$ orgasm (women)

**Figure**: estradiol (valeriate 10 mg) IM inj. 1x/month $\uparrow$ the frequency of coitus & orgasm in oophorectomized women (total abd. hysterectomy & bilateral salpingo-oophorectomy approx. 4 yrs ago) esp. in the postinj. weeks (Schiavi BB et al. Psychosomatic Medicine 1987, 49: 397-409)
## Testosterone & Estradiol Treatment in women → sexuality

<table>
<thead>
<tr>
<th>Women W/ estradiol implant</th>
<th>Women w/estradiol/testosterone implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexuality</td>
<td>greater</td>
</tr>
<tr>
<td>Activity</td>
<td>greater</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>greater</td>
</tr>
<tr>
<td>Leisure</td>
<td>greater</td>
</tr>
<tr>
<td>Orgasm</td>
<td>greater</td>
</tr>
<tr>
<td>Relevancy</td>
<td>greater</td>
</tr>
<tr>
<td>Virilizing effects</td>
<td>no</td>
</tr>
</tbody>
</table>

Table: comparison between women treated during 2 years w/ implants of estradiol alone  
*(Davis SR et al., Maturitas. 1995, 21: 227-236)*
Estradiol increases orgasm

Figure: many women complaining of sexual dysfunctions & estrogen deficiency are successfully treated with estradiol trans-dermal patch alone.

Higher testosterone levels => better orgasmic capacity with the partner

SUBJECTS: 999 women (age range 41-60 years) => 60 healthy women with 1 or more years of amenorrhea, without hormone replacement therapy and with a partner capable of intercourse

TREATMENT:

RESULTS: better sexual satisfaction:
• good self-esteem (p< 0.01)
• first orgasm obtained by masturbation (p = 0.004),
• major personal income (p = 0.007)
• sexual initiation in adulthood (p = 0.008)
• value physical contact with partner (p =0.021)
• major orgasmic capacity p = 0.040).

The following contributed towards orgasmic capacity with the partner:
• sexual initiation in adulthood (p = 0.012)
• regular physical activity (p = 0.040)
• higher testosterone levels (p = 0.050).

Hyperprolactinaemia

SUBJECTS: Women with hyperprolactinaemia

RESULTS:
80% of women with hyperprolactinaemia =>
• ↓ sexual drive
• inability to reach orgasm

Causes: ↑ prolactin levels =>
• ↓ of testosterone secretion by probably
• ↓ conversion of testosterone to dihydrotestosterone
• perhaps, direct effect of prolactin on the neurotransmitters involved in sexual activity

SUBJECTS: 26 postmenopausal women + sexual arousal disorder => questionnaires after taking either the drug or a dummy pill

RESULTS: Women on bremelanotide (vs placebo)
- 73 % of the bremelanotide => feeling genitally aroused (vs with 23 % + placebo)
- 43 % => augmented their sexual desire (vs only 19 % + placebo)
- slightly more likely to have sex with their partners during the course of the trial vs those in the control group, although who initiated the romps was not specified

CCL: Bremelanotide may well have some mild aphrodisiacal properties.
Quotes from Postmenopausal Women Treated with Bremelanotide

"Improvement in the quality of Climaxes: more intense, lasted longer, able to climax multiple times, more natural."

"Climax was more natural; like pre-menstrual"

"My climax was like it used to be"

"(Climax) quality was better - more intense, lasted longer."

"(Was) able to climax multiple times. That's not usual."

"Ability to orgasm was even easier than when I was 30"
Treatment for orgasm

Diet: avoid sweets, eat more fat (higher sex hormones and ovulation)

Hormone therapy

- **OXYTOCIN**
- **MELANOTAN II** (2X 0.3 mg/week) or bremelanotide
- Transdermal **Testosterone** gel 0.5%: ½ to 1 g/day (2.5 to 5 mg/day)
- Possibly 50 mg testosterone enanthate IM/month
- **Estradiol**/progesterone treatment
Sex in women

- Oxytocin
- MSH
- (Cortisol)
- DHEA,
- Testosterone,
- DHT

Estrogens