Using Testosterone in women

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Androgenic Options

- Implants – only licensed option until recently
- Oral – ? Liver effects
- Livial (tibolone)
- DHEA – weakly androgenic
- Injections – sustanon
- Gel – useful but not licensed
- Transdermal
Greenblatt
Robert Greenblatt
Am. J. Obstet & Gynecol 1949

Indications for the use of Testosterone implants

• Persistent menopausal symptoms in women receiving ERT

• In the woman who is not psychologically frigid and in whom increased libido is desired
Postmenopausal Woman - Libido

*Studd 1977 (BJOG)*

Uncontrolled study of 76 patients with psychosexual problems

- E50mg - effective for dyspareunia and improved libido in 80% patients

- Additional T100mg significantly improved libido in 12 out of 15 patients who had not responded to estradiol alone
Effects of testosterone

• 2-year single-blind, randomised trial in 34 women

• E50 vs E50 / T50 3-monthly

• E/T group significant ↑ in:
  - sexual activity
  - satisfaction
  - pleasure
  - orgasm

  *Davis et al; Maturitas, 1995*
Questionnaire of sexual and general health response in women receiving estradiol and testosterone implants

Hawkins A & Studd J 2004
What was the importance of loss of libido to you?

- **Sexual component**
  “made relationship difficult as not interested in sex”
  “libido almost zero”
  “inability to orgasm and feel satisfied”
  “no desire dead meat”

- **Non sexual component**
  “I felt my age”
  “lost self confidence – poor communication”
  “felt less capable”
  “others noticed that I had lost the “it” factor”
  “no creative drive”
  “I hated myself”
In what way has the treatment improved your sexual response?

• “can have easy orgasms and feel satisfied”

• “now feel like sex is part of my life again”

• “orgasms on train journey”

• “returned to normal”

• “like in my 20s with a bigger appetite –it’s wonderful”

• “initiate sex more orgasms”
Oral Testosterone
Oestrogen may not address all aspects of sexual function

Sexuality, Activity and Libido Scale assessed in menopausal women (n=20)
† p<0.01; ‡ p≤0.05

Effect on mood: Livial® versus placebo

Cross-over

Mean weekly sumscore (16 items)

Weeks

Tax et al., Maturitas
Effect on sexuality: Tibolone versus continuous combined HRT

Nathorst-Böörs et al., Maturitas 1997

McCoy sex scale

E₂/NETA, 17β-estradiol (2 mg/day)/norethisterone acetate (1 mg/day)
*p < 0.05 between groups
Testosterone gel

- Unlicensed for women
- 5ml gel 50mg sachet
- 0.5 – 1.0ml / day
- Abdo / inner thighs
- FAI up to 6.5%
Now, the love patch

A ‘Viagra’ to restore ladies’ joie de vivre

WOMEN could be wearing stick-on patches to boost their sex drive within months, say researchers.

The patches release the male sex hormone testosterone to help women overcome a loss of desire. Some experts claim it will be the female version of Viagra, with the latest research showing it can enhance libido and increase the amount of sexual activity enjoyed by women.

Men suffering impotence can already use a testosterone patch. The new patch could be available to women under licence. If approved, it would cost around £20 a month, and be Britain’s first male hormone patch.

From Jenny Hope:

Medical Correspondent, in Philadelphia, found in menopausal women who have been diagnosed with hypoactive sexual desire disorder (HSDD), in which libido and sexual activity is reduced, leading to psychological distress.

Altogether 607 women took part in a six-month study, with half using the active patch. As well as boosting the amount of getting it, the drug also increased desire.

COMING off the Pill can boost women’s sex drive, according to research.

Taking the hormonal contraceptive causes a loss in sexual desire in one in six women, scientists claimed yesterday.

Four weeks after abandoning the Pill, women who had complained of a lack of desire found their appetite for sex returned.

They had increased their libido, sexual and orgasm, according to a report at the American Society for Reproductive Medicine conference in Philadelphia.

Not taking the Pill led to rising levels of the sex hormone testosterone and a fall in a hormone that can suppress desire.

Experts believe that the loss of sexual appetite experienced by some women on the Pill may be triggered by the elimination of ovulation - nature's way of telling women to have sex.

Researcher Dr Susan Saffer, of the University of California, Los Angeles, said: 'Discontinuing hormonal contraception should be considered a first-line treatment for women complaining of sexual dysfunction.

Around 15 per cent of women taking the Pill, injectables or using a hormonal patch have symptoms of sexual dysfunction such as sexual distress, low libidos and lowered desire, she added.

In a pilot study, 20 women aged around 30 stopped taking the Pill after six months. Their sex life improved significantly, with increases in sexual appetite and orgasms, and a cut in sexual distress.

A larger study involving 200 women is now under way.

Dr Marian Damswood, president of ASRM, said: 'This study presents evidence for an effect many women are familiar with. When a healthy pre-menopausal woman experiences decreased sexual function, hormonal contraception could be considered as a possible cause and may be discontinued to determine whether it is indeed a factor.'
Intrinsa
(testosterone transdermal patch)

A new treatment option for surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen (not CEE)
Two studies in over 1000 surgically menopausal women

Safety and efficacy of a 300 mcg/day testosterone transdermal patch (TTP) in surgically menopausal (SM) women with hypoactive sexual desire disorder (HSDD) on concomitant oestrogen

- 1,095 women in 2 Phase III Trials (INTIMATE SM 1 and INTIMATE SM 2)
- 24-weeks of treatment
- Women aged 20 – 70 years with bilateral oophorectomy & hysterectomy
- Women receiving concomitant oestrogen

- Thin, clear, oval transdermal patch
- Twice-a-week application to abdomen

HSDD key parameters: desire, distress, sexual activity

Primary Endpoint:
- Change in frequency of total satisfying sexual activity from the Sexual Activity Log (SAL©)

Secondary Endpoints Included:
- Change in the Seven (7) Domains from the Profile of Female Sexual Function (PFSF©)
  - Desire
  - Arousal
  - Orgasm
  - Pleasure
  - Concerns
  - Self-Image
  - Responsiveness
- Change in distress with the Personal Distress Scale (PDS©)
- AEs and clinical labs

Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
Significantly increased sexual desire

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- SM1: 29% increase (p=0.0006)
- SM2: 18% increase (p=0.001)

Mean change from baseline

% Increase From Baseline

*All women received concomitant estrogen therapy

Buster J. et al., Obstetrics & Gynecology 2005;105;944-52
Intrinsa improves all domains of Profile of Female Sexual Function (PFSF)

Significantly reduced distress due to low sexual desire

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- **SM1**
  - 65% decrease
  - 40% decrease
  - \( p = 0.0006 \)

- **SM2**
  - 68% decrease
  - 48% decrease
  - \( p = 0.009 \)

Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52

*All women received concomitant estrogen therapy*
Significantly increased satisfying sexual activity

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- SM1: 33% increase, p=0.0003
- SM2: 23% increase, p=0.001

All women received concomitant estrogen therapy.
Continuous treatment for at least 3 months for maximal benefit – total satisfying activity

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

Analysis combined Intimate SM1 & SM2

*All women received concomitant estrogen therapy

Kingsberg S et al. Poster presentation at the Annual Meeting of the American Obstetrics and Gynecology Society, May 2005
Continuous treatment for at least 3 months for maximal benefit – sexual desire

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

* * p< 0.05

§Analysis combined Intimate SM1 & SM2

*All women received concomitant estrogen therapy

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Continuous treatment for at least 3 months for maximal benefit – sexual distress

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

* p< 0.05

§ Analysis combined Intimate SM1 & SM2

Kingsberg S et al. Poster presentation at the Annual Meeting of the American Obstetrics and Gynecology Society, May 2005
Testosterone patch clinical trials: Focus on relevant safety areas

In addition to adverse event reporting, the following parameters were assessed:

- Androgenic effects
  - Acne, Hirsutism, Alopecia, Voice Deepening
- Weight
- Blood Pressure
- Liver Function
- Haematology
- Lipids
- Carbohydrate Metabolism
- Cardiovascular Disease
- Breast Cancer
- Application Site Reactions

Buster J. et al., Obstetrics & Gynecology 2005;105;944-52
P&GP Data on file - ES02-2005
Overall Adverse Events (AE) profile

<table>
<thead>
<tr>
<th>Adverse Event (%)</th>
<th>INTIMATE SM1 Placebo (N = 279)</th>
<th>INTIMATE SM1 TTP (N = 283)</th>
<th>INTIMATE SM2 Placebo (N = 266)</th>
<th>INTIMATE SM2 TTP (N = 266)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AEs</td>
<td>79.6</td>
<td>77.7</td>
<td>74.1</td>
<td>74.4</td>
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<tr>
<td>Serious AEs</td>
<td>2.5</td>
<td>2.5</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Withdrawal due to AEs</td>
<td>6.8</td>
<td>8.5</td>
<td>8.3</td>
<td>8.3</td>
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<tr>
<td>Most Common AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application Site Reaction</td>
<td>39.1</td>
<td>31.1</td>
<td>28.9</td>
<td>29.7</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>24.4</td>
<td>21.9</td>
<td>19.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Unwanted Hair Growth</td>
<td>6.5</td>
<td>5.7</td>
<td>5.3</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
P&GP Data on file - ES02-2005
Safety focus: Androgenic AEs

<table>
<thead>
<tr>
<th>Androgenic AE (%)</th>
<th>INTIMATE SM1</th>
<th>INTIMATE SM2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 279)</td>
<td>TTP (N = 283)</td>
</tr>
<tr>
<td>Acne</td>
<td>6.1</td>
<td>6.0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Unwanted Hair Growth</td>
<td>6.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Voice Deepening</td>
<td>2.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Withdrawal due to Androgenic AE</td>
<td>0.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Buster J. et al., Obstetrics & Gynecology 2005;105;944-52
P&GP Data on file - ES02-2005
Safety focus: Androgenic AEs

<table>
<thead>
<tr>
<th>Androgenic AE (%)</th>
<th>Placebo (N = 545)</th>
<th>TTP (N = 549)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>5.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Unwanted Hair Growth</td>
<td>5.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Voice Deepening</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Withdrawal due to Androgenic AE</td>
<td>0.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
P&GP Data on file - ES02-2005
“What makes you think the hormone replacement therapy is having side effects, Mrs Brown?”
Free Testosterone levels following 24 weeks of treatment

Study Visit

- Placebo*
- Transdermal testosterone patch*

*All women received concomitant estrogen therapy

Whiskers describe the 10th and 90th percentiles; dots represent the median values.
Dashed lines denote reference ranges in premenopausal women (0.9 – 7.3 pg/mL)

Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
Conclusions from the testosterone patch phase III studies

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- The 300 mcg/day testosterone patch significantly improved desire and personal distress at 24 weeks.
- The testosterone patch significantly increased satisfying sexual activity at 24 weeks.
- The testosterone patch was generally well tolerated.

Buster J. et al., *Obstetrics & Gynecology* 2005;105;944-52
Clinical Lab and Vital Signs Summary
(SM1&2 Months 6-36 Open Label)

- No Significant effect on:
  - Blood Pressure
  - Triglycerides
  - Total Cholesterol
  - Alkaline Phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase or Total Bilirubin

- Over 3 years, patients experienced a small weight gain of 1.7 kg (p<0.05)

Nachtigall et al., NAMS, 2006
Over 36 months in surgically menopausal women with hypoactive sexual desire disorder (HSDD)†, the 300 mcg/day testosterone transdermal patch:

- Was well tolerated and
- No clinically relevant safety concerns were detected

† receiving concomitant oestrogen

* The absence of a parallel placebo treated control group limits our ability to draw definitive conclusions from these data

Nachtigall et al., NAMS, 2006
Considerations before use

In surgically menopausal women with Hypoactive Sexual Desire Disorder (HSDD) on concomitant oestrogen:

- Intrinsa is not recommended in women over 60
- The safety of Intrinsa has been demonstrated in randomised studies up to 1 year and open label up to 3 years
- ‘Continued use of Intrinsa is only recommended while concomitant use of oestrogen is appropriate’
- Intrinsa treatment response should be evaluated within 3-6 months of initiation, to determine if continued therapy is appropriate
- Intrinsa should not be used in women on conjugated equine oestrogen (CEE), as the trial subgroup of patients receiving CEE did not demonstrate a sig. improvement in sexual function.
Oestrogen Effect on Total Satisfying Sexual Activity at Week 24†
(SM1&2 Weeks 0-24 Double-blind)

†Combined SM Phase IIb, III Studies
*p<0.05
Testosterone Patch for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in naturally menopausal women: results from the INTIMATE NM1 study

Jan L. Shifren, MD,1 Susan R. Davis, MD,2 Michele Moreau, MD,3 Arthur Waldman, MD,4 Celine Bouchard, MD,5 Leonard DeRogatis, PhD,6 Christine Derozo, MD,7 Patricia Bearman, MD,8 Norman Kakos, MD,9 Sheila O’Neill, MD,10 Stephen Levine, MD,11 Kathryn Wekselman, PhD,12 Akhshay Bucq, PhD,12 Cynthia Rodenberg, PhD,12 and Robin Kroll, MD13

ABSTRACT

Objective: To evaluate the efficacy and safety of a testosterone patch for the treatment of women with hypoactive sexual desire disorder after natural menopause.

Design: A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted in naturally menopausal women with hypoactive sexual desire disorder receiving a stable dose of estrogen with or without progesterin (N = 568). Women were randomized to receive testosterone 300 µg/day or placebo patches twice weekly for 24 weeks. The primary efficacy measure was change from baseline in frequency of total satisfying sexual activity over a 4-week period (weeks 21–24).

Results: A total of 483 women (86%) were included in the primary analysis population (those with baseline sex hormone binding globulin levels ≤160 nmol/L). The change from baseline in number of total satisfying sexual episodes was significantly greater for testosterone compared with placebo (participants with baseline sex hormone binding globulin levels ≤160 nmol/L, mean change of 2.1 ± 0.28 versus 0.5 ± 0.23 episodes/4 weeks, P < 0.0001; intent-to-treat population, mean change from baseline of 1.9 ± 0.26 versus 0.5 ± 0.21 episodes/4 weeks, P < 0.0001). Testosterone also produced statistically significant improvements compared with placebo in all secondary efficacy measures, including sexual desire and personal distress. The testosterone patch was well tolerated.

Conclusions: Testosterone patch treatment increased the frequency of satisfying sexual activity and sexual desire, decreased personal distress, and was well tolerated in naturally menopausal women with hypoactive sexual desire disorder.

Key Words: Transdermal testosterone – Hypoactive sexual desire – Natural menopause – Postmenopausal women – Libido.
Increased Total Satisfying Sexual Activity at 24 Weeks

Testosterone compared to placebo

* Testosterone compared to placebo
Conclusions

• Evidence for benefits of testosterone in oestrogen replete women in both SM and NM women

• Initially only testosterone pellets available …

• Now, transdermal testosterone licensed in surgically menopaused women with HSDD using concomittant oestrogen.

• Published data exist for the effect of transdermal testosterone in naturally menopausal women

• Off label use of product should be confined to specialists at present
Some patients report persistent tiredness, lack of energy, reduced libido or sexual function despite apparently adequate doses of oestrogen replacement. This may be more common in oophorectomized women, and consideration should be given to additional treatment with testosterone.

(Management, Section 2. Hormone replacement therapy)