

## Letters sent to the FDA Advisory Committee opposing the approval of Intrinsa

To: Advisory Committee for Reproductive Health Drugs  
Food and Drug Administration,

I would like to express my concern regarding the testosterone patch for low desire in women who have had their ovaries removed. I was surprised and appalled to hear that the drug will come before the advisory committee after so little research on either its efficacy or its safety!

There is little agreement about what constitutes female sexual dysfunction, much less the best strategy to help women. Even those women who do have dissatisfaction about their sexual functioning and would like to take medication for it would be ill-advised to use this patch. There is no convincing proof that the patch will help them nor has there been a long term study to prove that it will not harm them.

Previously the FDA withheld approval of menopausal hormones for the prevention of heart disease because there had been no long term randomized trial showing efficacy or safety. When proper trials were carried out, these hormones were found to cause net harm to women. Please be just as prudent with the testosterone patch!

Sincerely,

Vicki Meyer, Ph.D.  
Founder, The InterNational Organization to Reclaim Menopause.  
www.inorm.org

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Advisory Committee for Reproductive Health Drugs  
Food and Drug Administration, HHS  
Re: the testosterone patch for women

Dear Committee Members,

As a sociologist who has engaged in extensive study of the medical management of sexuality, with a particular interest in midlife and late-life sexuality, I urge you to proceed with caution in recommending Proctor and Gamble's "Intrinsa" patch for approval. The FDA is a highly regarded body in the international community, and your actions will have influence far beyond your borders.

In the present case, a massively funded and well-orchestrated public relations campaign on the part of industry will make extravagant claims about the extent of “female sexual arousal disorder” and the wonders of the testosterone patch in treating it. These claims, however, far exceed the evidence available on benefits and risks. Furthermore, while the current application is based on evidence from trials involving surgically menopausal women, even a cursory review of the manner in which hype over the testosterone patch for women has already been taken up by both its promoters in the medical community and the popular media leaves no doubt that, should it be approved, off-label prescribing to all sorts of women will become commonplace. “FDA approved” will quickly become a marketing slogan to advance this agenda.

Surely we can learn something from the history of hormone replacement in men and women. The Women’s Health Initiative was so concerned about emerging evidence of health risks of HRT that it terminated a long-term study in post-menopausal women in 2002. Thus, after almost 2 decades of confident prescription of HRT to older women, we were forced to face the evidence. The National Institute of Medicine’s comprehensive report on testosterone supplementation in men, published in April of 2004, concluded that the growth in use of testosterone far outpaced the evidence of its benefits and risks. The latter case is particularly germane here, as testosterone supplementation is only FDA approved for hypogonadism in men, but the review of prescribing data revealed that it is prescribed at a rate which far exceeds the clinical incidence of hypogonadism. Testosterone supplementation is now widely marketed to middle-aged men as a treatment for a collection of symptoms collected under the rubric of “androgen deficiency in the aging male”, including decline in libido, decreased sports performance, grumpiness, and fatigue. This is precisely the pattern that we can expect should the “Intrinsa” patch be approved by the FDA.

There is no doubt that women and men, including those in mid- and late-life, experience sexual difficulties and problems which cause distress and affect their quality of life. Pharmaceutical remedies may, in fact, be appropriate elements in a plan to treat these. The approval of the current application, however, has implications far beyond the application of a specific remedy to a specific problem. To date, the clinical evidence is not sufficient to justify the opening that an approval of the testosterone patch for women will provide to the pharmaceutical industry for the broad-brush marketing of “female sexual arousal disorder” as a testosterone deficiency that will undoubtedly ensue. The health and well-being of a much larger population of women those who fit the profile of the clinical trial participants is at stake here.

Sincerely,  
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DATE: November 28, 2004

TO: Advisory Committee for Reproductive Health Drugs  
Food and Drug Administration, HHS

FROM: Maureen C. McHugh, Ph.D., [mcmchugh@IUP.edu](mailto:mcmchugh@IUP.edu)  
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Indiana PA

Re: Hearings on Intrinsic

As an educator who teaches courses on Human Sexuality I am urging the Food and Drug Administration to deliberate on the merits on Intrinsic in the larger context of how the marketing of this drug may impact on women's sexual health.

As indicated by the public relations campaign mounted by Proctor & Gamble to date we can expect the Proctor and Gamble and the media to: exaggerate the benefits of the patch; inflate the pool of potential candidates (to all women with low sexual desire); minimize the potential for harm from hormone use; and ignore the issue of conflict of interest when the supporting research is supplied by the producer of the product.

The research on the effectiveness of Intrinsic and its safety is not sufficient to begin marketing at this time. The research has been funded, designed and even conducted by the drug company manufacturing the patch. This research has not been submitted to the scientific community. It has not been peer reviewed. Further, the drug companies have not attended to or have misused existing research on the sexual experiences and desires of menopausal women.

For example in their press kit, Proctor and Gamble indicate that as many as 1 in 3 women experience low sexual desire, and that 40% of post menopausal women report a decline in sexual desire or a lack of interest in sex. There are no citations given for these statistics. Perhaps they are citing the research of Mansfield and her colleagues (Mansfield, Voda & Koch, 1995; Mansfield, Koch & Voda, 1998) who also found that marriage was a more important predictor of women's drop in sexual desire than was menopause. Life stressors and other contextual factors are likely to impact women's sexual functioning at midlife (Mansfield, Voda & Koch, 1995) including prevailing cultural prescriptions regarding sexual activity in later life. In a study of women's sexual response at midlife, Mansfield and her colleagues (Mansfield, et.al., 1998) found that for the 40% who reported changes in their sexual response, most women reported less sexual interest, but about one fourth of the women actually reported an increase in sexual desire and response, and more than one half of the research sample would like more non genital touching. In their study Mansfield and her colleagues (Mansfield, et. Al., 1998) found that women wanted more changes for themselves than for their husbands. While sexual responsiveness and more

desire figure in the list of desired changes, one can also see the women's needs for more fulfilling sexual relationships reflected in their lists. Women wanted to become: more passionate; more interested in sex; more romantic; more affectionate; more communicative; more sexually responsive; more desirous of sex; more initiating; more fun; more creative; less boring; more loving; and less inhibited. They wanted their husbands to become: more communicative; more romantic; more affectionate; more fun; more passionate; more loving; more creative; and less boring. Treatments like the patch are likely to focus on changes in sexual responsiveness while ignoring women's desire for more communication and affection. Similarly, Ellison (2001) concluded, based on her survey results, that women associate sexual satisfaction in relationships with closeness, love, acceptance and safety, and that sexual problems and concerns of women often center on intimacy and relationship issues.

There are not only many problems, but there are many different causes and contributing factors for women's sexual problems. Not only are these problems unlikely to be resolved by a pill or the testosterone patch, but the marketing of the patch will emphasize the physiological processes and will discount the role of other factors such as lack of sexual information, cultural attitudes and messages, fatigue, partner and relationship issues, and psychological factors like depression and anxiety.

I am concerned that women who do not experience desire for genitally-focused, male-oriented, penetrative, and/or non-affectionate sex will be urged to wear a patch to correct "their" problem. I advocate that research on the patch be conducted in the context of research that examines what women want in terms of sexual experiences and relationships.

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To the Advisory Committee for Reproductive Health Drugs  
Food and Drug Administration, HHS:

I understand that you are in the process of holding hearings on the Procter & Gamble testosterone patch (Intrinsa) for the treatment of Hypoactive Sexual Desire Disorder in women who have undergone surgical oophorectomy.

I have practiced gynecology for over twenty years and, having given up obstetrics over ten years ago, take care of a large population (thousands) of peri- and post-menopausal women. Over these years we have all witnessed the changes that have taken place with regard to findings on the efficacy and safety of hormone replacement therapy (HRT) consisting of estrogen and a progestin. It was considered gospel when I started my practice that HRT would benefit almost all menopausal women. Physicians and the public alike were advised that it should be considered to reduce the risk of numerous conditions, most importantly cardiovascular disease, the leading cause of death of women as well as men. It wasn't until many years of a controlled study of over one hundred thousand women by the Women's Health Initiative that the risks of HRT as a

contributory agent in cardiovascular disease as well as breast cancer were delineated and quantified. On the day that the WHI's findings were released in the press I received over 100 phone calls from panicked women. They described feeling "betrayed," like "guinea pigs" of a male dominated scientific community who cared less about their safety and long term health than about the profits of drug companies.

I fear that history is about to repeat itself. On Saturday, November 20<sup>th</sup>, 2004 I attended a conference "Renewing Sexual Desire: understanding HSDD in postmenopausal women." Of the three panelists, two had received grant and research support from Procter & Gamble. One was a general consultant for the company and the other was on its Speaker Bureau. The basic premise of the conference was that menopause was an androgen insufficiency state. The off-label use of the testosterone patch was being heavily promoted as a treatment for all menopausal women with a wide variety of symptoms including: reduced energy level, unexplained fatigue, and "diminished sense of well-being," as well as decreased libido. Safety factors were glossed over, and although the panelists admitted that there were no long-term data on increased risks of cardiovascular disease or malignancy, course participants were told that there was "unlikely" to be any significant increase in risk because the dose used in the patch produced blood levels within the "physiologic" range. They conveniently neglected to mention that if this is being used in post-menopausal women, the levels produced are not in the "physiologic" range for them.

The safety and efficacy of long-term testosterone therapy for women in association with ERT or HRT have not been sufficiently established to warrant its approval at the current time. Will the addition of testosterone synergistically increase the risks of cardiovascular disease or malignancy in treated women? Will we find late adverse effects when testosterone is mass-marketed that were not found in the relatively small and short-term studies conducted? Is a decrease in sexual desire a natural consequence of aging in some, just as decreased exercise tolerance is, and not a "disorder?" Few eighty year olds run marathons yet we don't speak of "hypo-marathon disorders."

Many women feel that the medical community let them down by not questioning persistently enough and strongly enough the rationale that prescribed HRT for so many of them. Although there certainly is a wide demand for that "magic drug" that will enable one to maintain youth, beauty, energy, and sexual vitality forever, I would strongly urge the FDA to put on the brakes. Insist on further and longer testing of Intrinsa to assure its safety and efficacy. There should be independent double blind controlled studies of large numbers of women in different age groups looking at efficacy measured objectively (self-reported frequency of woman initiated sexual experiences, for example) as well as subjectively reported. Differences between the control groups and groups receiving testosterone should be look at with regard to the risk of cardiovascular disease and malignancies of the female reproductive tract, as well as the liver,

bladder, and other organs, including melanoma. Differences in cognitive function and the incidence of Alzheimer's disease between the two groups should be looked at as well.

Let's take the information we learned from the WHI with regard to the sometimes unexpected effects of HRT on multiple organ systems and apply it to studies of the hormone testosterone. Resist the temptation to succumb to the demands of Procter & Gamble that possibly millions of women be unwitting subjects in yet another uncontrolled study of the effects of yet another hormone therapy. A slide at the referred to conference indicated that there are over 42 million American women 50 years of age or older – 1 out of 3 women. This is P&G's true target population. If you resist this premature approval, in the end, women will be grateful that you took their health issues seriously and that you valued their well-being more than drug company profits. There is so much skepticism and concern currently about the motives of pharmaceutical companies and the ability and willingness of the FDA to properly regulate drugs and protect the public. I urge you not to provide more grounds for cynicism.

Sharon B. Diamond, MD  
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I am an Assistant Clinical Professor at Mount Sinai School of Medicine.

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Advisory Committee for Reproductive Health Drugs  
Food and Drug Administration, HHS  
C/O Ms. Watkins and Ms. Somers, Staff  
Re: upcoming hearing on the use of testosterone for low sex desire in women  
Dear Advisory Committee:

As researchers in the area of human sexuality, we have become aware that you will be holding hearings to discuss Procter and Gamble's proposed testosterone patch for low sexual desire in women.

We are writing to oppose such an approval at this point, given the lack of knowledge concerning the long-term safety and efficacy of this drug in humans.

A substantial literature exists on the use of postmenopausal hormone therapies to enhance female sexual functioning.

A recent review by Alexander et al. entitled:

The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. Menopause. 11(6) Supplement:749-765, 2004.

Alexander, Jeanne Leventhal MD, FABPN, FRCPC 1; Kotz, Krista PhD, MPH 2; Dennerstein, Lorraine AO, MBBS, PhD, DPM, FRANZCP 3; Kutner, S. Jerome PhD 4; Wallen, Kim PhD 5; Notelovitz, Morris MD, PhD 6

Has the following abstract:

Double-blind randomized controlled trials of estrogen and/or testosterone on sexual function among natural or surgical menopause in women are reviewed. Power, validity, hormone levels, and methodological issues were examined. Certain types of estrogen therapy were associated with increased frequency of sexual activity, enjoyment, desire, arousal, fantasies, satisfaction, vaginal lubrication, and feeling physically attractive, and reduced dyspareunia, vaginal dryness, and sexual problems. Certain types of testosterone therapy (combined with estrogen) were associated with higher frequency of sexual activity, satisfaction with that frequency of sexual activity, interest, enjoyment, desire, thoughts and fantasies, arousal, responsiveness, and pleasure. Whether specific serum hormone levels are related to sexual functioning and how these group effects apply to individual women are unclear. Other unknowns include long-term safety, optimal types, doses and routes of therapy, which women will be more likely to benefit from (or be put at risk), and the precise interplay between the two sex hormones.

This suggests that much is not known regarding the effects of hormone levels on female sexual functioning, particularly supraphysiological dosages of testosterone.

We would suggest that to approve testosterone patches for use in women would lead to more widespread use before further studies can be done to assess the effects, side effects, risks and benefits of this drug.

A more prudent approach would be to not approve this drug for this purpose at this time and instead to insist on further study.

Thank you for your attention to this matter.

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& Meg S. Kaplan, Ph.D.  
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