Testosterone therapy for reduced libido in women

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***Abstract*:** Modest benefit has been shown from transdermal testosterone therapy given to postmenopausal women with reduced sexual desire. An increased frequency of satisfying sexual encounters and intensity of sexual desire and response has been shown in medically and psychiatrically healthy women able to have 2–3 satisfying sexual experiences each month before therapy commences. Women more clearly sexually dysfunctional in keeping with currently proposed definitions of sexual disorder have not been studied. Numerous factors are known to influence women's sexual desire with mood and feelings towards the partner showing the most robust associations. How to identify women whose low desire might stem from low testosterone activity remains unknown: neither serum levels of testosterone nor its metabolites correlate with desire or function. Production of androgens in the brain, sensitivity of the androgen receptors, and activity of cofactors are all potentially relevant confounds. The long-term safety of systemic testosterone with or without estrogen is unknown but necessary as women's sexual lives tend to endure as long as there is an active partner.

***Keywords*:** libido, sexual dysfunction, testosterone, women's sexual desire

Introduction

Sexual response is a complicated affair: that it is a response rather than an innate force is sometimes forgotten. The stimuli needed to trigger the emotions we label as desire and arousal, as well as the physical responses of the body, are highly variable, influenced not only by experience but by culture, morality, newness *versus* sameness, uncertainty *versus* predictability. The individual's openness in attending to the sexual stimuli to allow the mind's conscious and unconscious appraisal, adds further levels of complexity. This appraisal and subsequent responding involves numerous neurotransmitters and peptides, themselves modulated by, and interacting with sex hormones, most notably testosterone.

An ongoing question of major clinical importance has been whether a relative lack of testosterone activity underlies women's sexual dysfunction. The latter has been traditionally divided into disturbances or disorders of particular phases of response, that is, desire, arousal, and orgasm. However, the data from many large epidemiological studies are clear: comorbidity of these three disorders is the most common presentation, sometimes described as a 'blunting' of the whole response [Sanders *et al.* 2008; Hartmann *et al.* 2004; Slob *et al.* 1996; Bozman and Beck, 1991]. This is characterized by minimal desire stemming from thoughts or fantasies, or in response to stimuli in the environment; muted arousal during sexual stimulation, such that desire cannot be triggered even during the sexual experience; and given the low arousal, little likelihood of orgasm.

Transdermal testosterone therapy for surgically postmenopausal estrogenized women complaining of low sexual desire since that surgery is approved in some countries. In North America, in the absence of such approval, off-label prescription of testosterone is widespread [Snabes and Simes, 2009], and is not limited to surgically menopausal estrogenized women. This review aims to summarize the evidence supporting testosterone prescription to women as well as the uncertainties that may underlie the lack of its approval by the US Food and Drug Administration (FDA) and the current recommendation against its use by the American Endocrine Society [Wierman *et al.* 2006] and the UK *Drug and Therapeutics Bulletin* [DBT, 2009].

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Sexual libido, desire and motivation

Whether reduced 'libido', usually taken as synonymous with sexual desire, should be considered a medical disorder is far from clear. Epidemiological data confirm that women of different ethnic origins often report satisfactory sexual lives despite rarely or never sensing sexual desire either at the outset or between sexual encounters [Cain *et al.* 2003]. Both women and men report very many reasons for engaging in sexual activity with a partner, desire being an important one, but as many as 237 reasons to engage were recently identified [Meston and Buss, 2007]. These 237 discrete 'reasons for sex', identified by 3000 mostly young men and women, were divided into four domains: love and intimacy; pleasure (where desire/libido would fit); 'mate guarding' (preventing loss or impairment of the relationship); and nefarious reasons (e.g. to gain job promotion, or for money).

It is clear that women can begin an ultimately rewarding sexual encounter for one or many reasons that may or may not include an initial awareness of desire/libido. The latter appears to be more common in newer relationships and in younger women [Klusmann, 2002]. A motivational model of sexual response is currently considered to depict most accurately the human condition [Toates, 2009; Wylie and Mimoun, 2009; Sanders *et al.* 2008; Basson, 2006, 2000; Janssen *et al.* 2000]. As shown in Figure 1, there are a number of reasons for an increase in a person's willingness to attend to sexual stimulation that potentially can give sexual pleasure and arousal/excitement along with physical changes including genital vasocongestion. The mind's appraisal of the sexual stimuli comprises both a reflexive element (in women the vulval swelling and vaginal lubrication) and a slower appraisal leading to subjective (mental) arousal, which in turn triggers desire such that the two emotions overlap. Many factors modulate this appraisal, potentially limiting or precluding subjective arousal and associated desire. Low mood, low self-image, fear of appearing sexually substandard, fear of negative outcome, negative feelings towards the partner [Bancroft *et al.* 2003; Dennerstein *et al.* 2001], along with sexual and nonsexual distractions, all of which can interfere [Sanders *et al.* 2008; Basson, 2006]. Fatigue, debility, depression [Clayton *et al.* 2007], and medications including most antidepressants [Basson *et al.* 2010], can also preclude subjective arousal. Testosterone deficiency is also suspected to negatively influence this appraisal but definite proof is lacking. As will be discussed later, women recruited to randomized controlled trials (RCTs) of transdermal testosterone therapy were already able to be aroused and have satisfying sexual encounters some 2–3 times a month before any therapy was given [Basson, 2006].

It is also apparent from Figure 1 that initial or seemingly 'spontaneous' desire can augment the circular response cycle at many points. Some researchers label this component as 'sexual drive' [Wylie and Mimoun, 2009]. When present, it will certainly augment the initial motivation but also increase the willingness to focus on the sexual stimulation such that arousal is much more predictable. It is important to note that the cycle is typically experienced many times in any one sexual encounter: a small degree of arousal or desire once triggered will cause the woman to ask for/accept more intense sexual stimulation leading to more intense arousal and desire. Direct, initial genital stimulation is typically unwelcome and unrewarding when the woman is sexually neutral and motivated for other reasons, for example, to enhance intimacy and commitment or to feel better about herself, more attractive and even more 'normal'.

Figure 1 also depicts arousal and desire as overlapping entities. Qualitative research confirms a majority of women do not clearly distinguish the

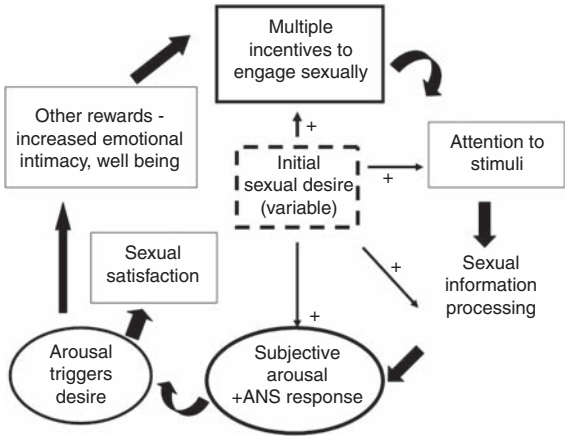

Figure 1. Incentives model reflecting the many reasons to begin a sexual encounter: The brain's appraisal 'information processing' of relevant sexual stimuli allows the emotions of arousal and desire to be accessed. Desire 'drive' at the outset is advantageous and will reinforce the cycle at many points but its absence does not denote disorder *per se*. (Reproduced with the permission of Lippincott, Williams and Wilkins from Basson [2001]).

two [Graham, 2010; Brotto *et al.* 2009]. Thus, some researchers now refer to the concept of 'triggers of desire', and their studies conclude that premenopausal and postmenopausal women identify multiple triggers [McCall and Meston, 2007]. It is important to note that it is the subjective component of arousal that merges with desire. That the physical changes of arousal and the subjective experience are separate entities has been emphasized by many, and their poor correlation in a majority of women has been repeatedly demonstrated during the past two decades [Chivers *et al.* 2010].

Recommendations for a revised definition of hypoactive sexual desire disorder (HSDD) were recently published by the American Psychiatric Association Review Committee for their *Diagnostic and Statistical Manual of Mental Disorders* (DSM) [Brotto, 2010]. To date, the definition of HSDD has depicted a minimal sense of sexual desire ahead of sexual engagement together with few or no sexual fantasies. Replacing HSDD is the proposed terminology 'sexual interest/arousal disorder' (SIAD), which requires an absence of ability to trigger desire during sexual activity as well as a lack of desire at the outset.

Reduction of testosterone production with age

Both ovarian and intracrine sources of testosterone are important contributors to the total testosterone activity in women. After natural menopause, ovarian testosterone production continues to a variable extent. Ovarian production of androstenedione (A_4) and dehydroepiandrosterone (DHEA), both of which can be converted in peripheral cells to testosterone and estrogen, is reduced. The adrenal glands are the major source of precursor hormones DHEA, DHEA sulfate, A_4 and androstene-3β, 17β-diol (5-diol), and these too decrease with age, by some two thirds between ages 30 and 70 years [Davison *et al.* 2005; Labrie *et al.* 1997]. Aging is associated with lessening of sexual desire but interestingly, not with an increased prevalence of HSDD [Hayes, 2008]. The latter is currently defined as deficient or absent sexual fantasies and desire for sexual activity causing marked distress or interpersonal difficulty. Older women can still enjoy their sexual lives despite reduction of spontaneous desire and importantly, they are not distressed by its lack. On the other hand, younger women who sense something is wrong with them, and report their distress, have been diagnosed with a sexual disorder. Whether the woman becomes distressed depends in part on the reaction of her partner, to lead to the curious and unsatisfactory situation that a partner's reaction can determine whether or not a woman is labeled as having a sexual disorder.

Sexual desire after surgical menopause

Whereas natural menopause *per se* does not alter intracrine or ovarian testosterone production, surgical menopause obviously removes all ovarian testosterone, ovarian DHEA and A_4 production. Interestingly, cross-sectional epidemiological data in HSDD show that surgically menopausal women are distressed by lowered desire more than are age-matched women with intact ovaries [Dennerstein *et al.* 2006; Leiblum *et al.* 2006]. However, they do not have a higher prevalence of low desire *per se* [West *et al.* 2008]. Moreover, prospective studies of elective bilateral salpingo-oophorectomy along with a necessary elective perimenopausal hysterectomy do not identify any decrease in women's sexual function when they are followed for up to 3 years [Teplin *et al.* 2007; Farquhar *et al.* 2006; Aziz *et al.* 2005]. It would seem the cross-sectional epidemiological studies likely include some women whose oophorectomies were unchosen to then impose infertility, and/or were associated with malignant disease. Thus, in some instances the thematic context of bilateral oophorectomies is likely to impair sexual desire and function.

Beyond ovarian and intracrine testosterone

It remains possible that testosterone deficit hinders desire and response but that its systemic production is of little relevance. Testosterone is produced *de novo* within the central nervous system starting from cholesterol [Melcangi *et al.* 2008]. This production appears to be quite widespread within the central nervous system. Adaptive changes occur in the brain to reductions in serum levels of sex hormones associated with age and with menopause: there is an upregulation of steroidogenic enzymes and sex receptors [Ishunina and Swaab, 2007]. How much this varies among women remains to be investigated. How supplemental testosterone might affect neurosteroid production is not known.

Another confound is the sensitivity of the androgen receptor: a length polymorphism in a repeated sequence of the androgen receptor gene has been reported to modulate the activity of the receptor [Li and Al-Azzawi, 2009]. However, the molecular structure of the

androgen receptor in women with and without sexual disorders has not been studied. Not only would relative resistance of the androgen receptor theoretically impair testosterone activity and contribute to sexual dysfunction, but this could be accompanied by relatively high serum testosterone levels due to lessening of the hypothalamic pituitary ovarian negative feedback. Moreover, supplemental testosterone would be unlikely to be of benefit. Variability in numbers and activities of the cofactors for the androgen receptor further clouds the issue.

Testosterone activity and women's sexual function

Given the loss of sexual desire in men along with the loss of nocturnal erections, ejaculate volume and ease of obtaining an orgasm are all associated with serum levels of testosterone well below the lower limit of normal, it is reasonable to consider whether testosterone lack in women modulates their sexual desire and function. We do not have sound scientific evidence that this is so. Serum levels of testosterone do not correlate with women's sexual function according to large epidemiological studies [Davis *et al.* 2005; Santoro *et al.* 2005]. It has been assumed that two confounds have precluded showing an association between low testosterone and women's sexual dysfunction. The first has been the difficulties with available assays that were originally designed to measure male range of testosterone. Studies using the more sensitive 'gold standard' assays, that is, those employing mass spectrometry, were expected to show a correlation between women's sexual function and serum testosterone so measured. However, a recent study of 121 women with HSDD and 124 control women found no group difference in terms of mass spectrometry-measured serum testosterone [Basson *et al.* 2010]. The second confound was the inability to measure intracrine testosterone until the last decade. Studies have now shown a wide range in androgen metabolites, most notably androsterone glucuronide (ADT-G), among women of any given age group [Labrie *et al.* 1997]. These metabolites reflect the total androgen activity, that is, ovarian plus intracrine. The expected decline in androgen metabolites with age has been confirmed. Recently, ADT-G levels were compared in 121 women with HSDD and 124 women without, and no group differences were found [Basson *et al.* 2010].

The testosterone patch studies

Surgically menopausal women

Over the past 5 years, seven parallel group RCTs of transdermal testosterone for medically and psychiatrically healthy postmenopausal women with low sexual desire have been published. These were all by the same sponsor and designed to raise testosterone levels to the high premenopausal range. Four involved surgically menopausal estrogenized women [Davis *et al.* 2006b; Braunstein *et al.* 2005; Buster *et al.* 2005; Simon *et al.* 2005]. The majority of women in the first three studies received oral estrogen whereas all in the fourth received transdermal formulations. The first trial found that 300 μg but not 150 or 450 μg of transdermal testosterone daily significantly increased the frequency of sexually satisfying events ($p = 0.049$) compared with placebo. Grouping these four studies together, at baseline the recruited women reported 2–3 sexually satisfying experiences per month and these increased to approximately five per month with active drug and to four per month with placebo. Using an unpublished validated questionnaire, scores in the desire and arousal scales were significantly increased by the active drug in the first three studies (for desire: $p = 0.05$ in the first study, 0.006 in the second, and 0.001 in the third). The fourth smaller study recruiting women prescribed transdermal estrogen showed significant increase in desire and response scales but not in the numbers of sexually satisfying events [Davis *et al.* 2006b]. Based on power calculations, this latter study aimed at recruiting 80 women to each arm but due to slow recruitment it stopped at 77 patients in total with 61 women completing treatment; data were analyzed on an intention to treat basis.

Naturally menopausal women

A study of 549 naturally menopausal women receiving oral estrogen and transdermal testosterone showed a statistically significant increase from baseline in the frequency of satisfying sexual events compared with placebo ($p < 0.0001$) [Shifren *et al.* 2006]. Also there were statistically significant improvements in the questionnaire scales for desire and response. Despite concurrent endogenous production of ovarian testosterone and ovarian precursor hormones, median levels of free and bioavailable testosterone remained in the normal range for premenopausal women. That total testosterone levels were above the normal range may have been at least in part due to increased sex

hormone-binding globulin levels associated with the concurrent oral estrogen therapy.

Estrogen-deficient menopausal women

Of 814 estrogen-deplete women randomized to 150 μg, 300 μg of transdermal testosterone or placebo, only 464 completed treatment with similarly high discontinuation rates in all three arms. A significant increase in satisfying events was seen in the naturally menopausal women from 300 μg of testosterone but not in the small surgically menopausal subgroup [Davis *et al.* 2008a]. The study was likely insufficiently powered for subgroup analysis. There were statistically significant improvements in the questionnaire scales for desire and response. Again, recruited women were experiencing 2–3 sexually satisfying episodes per month at baseline.

A further study of 272 naturally menopausal women of whom 73% were not receiving systemic estrogen, and reporting 2–3 rewarding sexual experiences per month before treatment, showed an increase of 1.69 satisfying episodes each month from the active drug compared with an increase of 0.53 from placebo [Panay *et al.* 2010].

A previous small study had shown minimal or no benefit from transdermal testosterone in estrogen-deficient women with a past history of cancer [Barton *et al.* 2007].

Postmenopausal women already have high testosterone to estrogen ratios compared with premenopausal women. Long-term sequelae of creating a distinctly nonphysiological profile of the testosterone:estrogen ratio are completely unknown. Certainly, endogenously high testosterone along with obesity in older women is associated with insulin resistance and increased cardiovascular morbidity [Wild, 2007].

Premenopausal women

There was minimal benefit from transdermal testosterone when given to premenopausal women in another recent study of 261 premenopausal women recruited on the basis of loss of their former sexual satisfaction [Davis *et al.* 2008b]. One of three doses aimed to increase free testosterone levels to the high normal range for premenopausal women showed statistically significant benefit at the chosen 16-week point. Women receiving the middle dose experienced 0.8 more sexual satisfying events in the previous month than women receiving placebo. No doses were associated with any improvement beyond placebo as measured by the validated sexual function and satisfaction questionnaire. A previous small crossover study of 31 women had shown benefit as measured by the same questionnaire recalling experiences over the last 4 weeks of a 12-week period of drug use [Goldstat *et al.* 2003].

Limitations of testosterone RCTs to date

A major drawback of the testosterone patch trials are the criteria for recruitment. It is not certain that the recruited women had any sexual disorder: the focus has been consistently on the frequency of satisfying events in women able to have such experiences. When clarified, it is apparent that some 50% of the women's experiences were satisfactory at baseline [Davis *et al.* 2006b]. Thus the subjects did not have consistent difficulties or dysfunctions, pointing against a biological cause or a need for a biological remedy, and pointing towards psychological, relationship or contextual factors, which are inherently variable. As noted, there was improvement in the secondary endpoints of desire and response subscales in the (unpublished) validated questionnaires used in all the trials. However, this desire scale may well have rewarded initial/spontaneous desire, whereas the epidemiological data are clear: this type of desire is but one aspect of sexual motivation; its absence frequently does not preclude sexual satisfaction and its lessening with relationship duration may be normative [Brotto, 2010; Cain *et al.* 2003]. Increasing the degree of pleasure and arousal currently experienced may not necessarily imply that absent pleasure and absent arousal would be remedied. Interestingly, tibolone with its androgenic as well as estrogenic and progestogenic activity was shown repeatedly to increase desire and response scores in sexually functional women recruited for nonsexual reasons for postmenopausal therapy, and yet, the recent RCT of sexually dysfunctional women showed benefit only comparable to that afforded by transdermal estradiol and norethisterone acetate [Davis *et al.* 2006a].

One of the co-authors of the testosterone patch studies has addressed the question of clinical relevance of the documented statistically significant benefit [Kingsberg *et al.* 2007], in women involved in two of the patch studies [Buster *et al.* 2005; Simon *et al.* 2005]. The study was underpowered given that it was estimated that 200 women would be needed to detect a 20% difference between the groups, whereas 132 women were studied. Some 52% of the women receiving

active drug reported 'meaningful treatment benefit' compared with 31% receiving placebo. On subanalysis of three areas (increase in sexual activity, increase in desire, whether treatment met expectations), differences were not significant. Confirming a meaningful therapeutic benefit in some women does not negate the concern that using current understanding of women sexual response [Brotto, 2010; Graham, 2010; Wylie and Mimoun, 2009], both pre- and post-therapy the women's sexual responses were 'within normal limits'. The typical psychological profile of women who present with desire concerns such that they are diagnosed with having HSDD must be borne in mind: even when carefully excluding women with clinical depression, there is evidence of higher numbers of depressed and anxious thoughts, more mood lability, and low self-image [Hartmann *et al.* 2004]. Put very simply: would happier mid-aged and older women be distressed to have only close to three sexually satisfactory sexual experiences per month?

The placebo response was robust as is expected when women believe their sexual lives are being assisted: they will be more willing to begin an encounter even when they are feeling sexually neutral, more willing to attend to the stimuli and focus on them, and to request those stimuli that are attractive to them. In one study the authors note that 'all women enrolled in our study stated that they desired an improvement in their sex lives and participation in the study may have increased the dialogue between study participants and their partners, leading to improvements in sexual satisfaction' [Braunstein *et al.* 2005]. As noted in the *Drug and Therapeutics Bulletin* [DTB, 2009], this comment undermines any idea that a hormonal deficit requiring rectifying was present.

Blinding of testosterone therapy trials is particularly difficult. Increased hirsutism can be easily hidden (by plucking). For many women, facial hair growth is a very private concern and disclosure is difficult. Moreover, the testosterone may be acting by increasing general well being and/or energy, and this may also limit blinding as well as offer a nonandrogenic reason for improvement.

A further complexity is the possibility that the improved mood (potentially even mania) [Weiss *et al.* 1999], rather than androgen action underlies the modest benefit in the testosterone patch RCTs. Robust association between low desire and depression has been repeatedly demonstrated [Lutfey *et al.* 2009; Avis *et al.* 2005; Bancroft *et al.* 2003; Kennedy *et al.* 1999]. Recent empirical research confirms that an experimentally induced happy or sad mood can impact subjective sexual arousal (but not objective vaginal congestion as measured by a vaginal photoplethysmograph), with subjects reporting significantly less subjective arousal and marginally significant fewer genital sensations when a negative mood was induced prior to viewing an erotic film clip [ter Kuile *et al.* 2010].

Whether the benefit continues well beyond 6 or 12 months is unclear. The only published data from women receiving testosterone for up to 3 years are in an abstract: of an unknown number enrolled into open-label extensions of two of the patch studies, just 12% completed the 3 years of therapy [Nachtigall *et al.* 2006].

Safety of long-term testosterone therapy

Long-term safety issues include those of the combination of testosterone and estrogen as well as current concerns about estrogen itself. The former are not known beyond 3 years. While most of the patch studies were of 6 months duration, women in two of the studies could enroll into open-label extensions. Only an abstract is available [Nachtigall *et al.* 2006]: it is not clear how many of the original 1094 enrolled but 21% completed 2 years and 12% completed 3 years. No clinically relevant changes in liver function, carbohydrate metabolism, lipids, clotting parameters or hematology were noted. No placebo group was followed simultaneously. Three cases of invasive breast cancer occurred, which was considered to be consistent with age-expected rates. There has been criticism that the target high normal serum concentrations of testosterone and dihydrotestosterone were exceeded in a significant number of women in the patch studies [Arlt, 2006]. Indirect data support both risk increase and decrease for breast cancer from testosterone supplementation: a recent review concludes that the available clinical literature does not permit conclusions on safety [Bitzer *et al.* 2008].

In contrast to the situation in men, women with high endogenous testosterone are more likely to develop insulin resistance and cardiovascular risk [Brand and van der Schouw, 2010; Wild, 2007], but how this relates to postmenopausal testosterone therapy is unknown.

Currently long-term estrogen therapy is not advocated. Women beginning estrogen therapy at menopause may show cardiovascular benefit rather than harm, but there is no evidence that after 10–15 years of exogenous estrogen supplementation endothelial function is preserved in a healthy state such that estrogen can be prescribed indefinitely to these women. Women's sexual lives however, tend to continue as long as they have a sexually active partner. Thus, the long-term safety of estrogen and testosterone received systemically is currently unknown but is crucial. For many of these reasons the American Endocrine Society currently advises against testosterone supplementation for women [Wierman *et al.* 2006]. Similarly the *Drug and Therapeutics Bulletin* was unable to recommend, the albeit licensed, testosterone patch in the UK [DBT, 2009].

Required RCTs

RCTs that recruit women unable to have any sexually satisfying experience are needed, that is, women who are motivated to sexually engage for any of the multiple 'nondesire' reasons women identify [Meston and Buss, 2007], but find that despite their willingness to focus on their sexual stimulation, no subjective arousal occurs, thus, no desire is triggered. Lack of attraction to the partner, negative feelings for the partner at the time of sexual interactions [Bancroft *et al.* 2003], and low mood should all be exclusion factors as well as the more obvious exclusions of clinical depression, relationship discord or interfering medications.

DSM definitions of women's sexual disorders are being revised currently [Brotto, 2010; Graham, 2010]. A detailed review of the data supporting the concept of a SIAD has been recently published [Brotto, 2010]. Specifically there needs to be an absence or paucity of desire initially and an absence or paucity of desire triggered during the sexual experience for this disorder to be diagnosed. Such changed definitions will clearly mandate different inclusion/exclusion criteria in subsequent trials of testosterone supplementation.

As well as including women with more definite dysfunction (SIAD rather than HSDD), trials must extend well beyond the typical 2–3 years of safety monitoring for all the reasons mentioned previously.

Beyond RCTs of testosterone

Given the wide range variables in the amount of hormone or precursor hormone produced in the activity of enzymes converting precursor hormones to active sex hormones, the sensitivity of the androgen and estrogen receptors, and the relative importance of neurosteroids *versus* systemic sex steroid production, individualized therapy taking these factors into account would be a future ideological goal.

Considering that testosterone and estrogen inherently possess many nonsexual actions, supplemental therapy may have a too high potential risk of adverse effects. The development of selective estrogen receptor modulators and selective androgen receptor modulators that have different agonist/antagonist actions on the androgen and estrogen receptors in different tissues carries promise in countering risk. This may lead to molecules conferring greater sexual benefit-to-risk ratios and added benefits on breast health, cardiovascular health, and glucose metabolism as well as the health of the endometrium and bone density.

Current use of off-label prescription of testosterone to women with low libido/desire

Some two million prescriptions for off-label compounded formulations of testosterone were written for women in 2006–2007 by American physicians [Snabes and Simes, 2009]. The uncertainty of long-term safety, particularly cardiac, precluded approval of transdermal testosterone by the FDA in 2004, but did little to reduce off-label prescribing. The situation is clearly of concern, particularly as no scientific monitoring of this extensive off-label prescription is likely to occur. It must be recognized also that women prescribed the various dosages of the various formulations of testosterone approved for men may not be receiving just 300 μg daily, with an unknown percentage receiving a considerably higher dose.

Local delivery of testosterone

Although clinicians sometimes prescribe topical testosterone to be used sparingly on the vulva in an attempt to restore lost sexual sensitivity of tissues comprising and overlying the clitoris, this practice has not been scientifically studied. Recently however, local delivery of the main precursor hormone, namely DHEA, into the vagina was reported to not only efficiently reverse estrogen deficiency-associated vulval vaginal atrophy, but to restore genital sexual sensitivity, such that orgasms were more easily obtained and more

intense [Labrie *et al.* 2009]. Moreover, the desire item on the questionnaire used in the study also improved significantly compared with placebo. This therapy appeared to be truly local as there was no increase in serum DHEA, estrogen or testosterone. Further study is needed to confirm these results. Although the term 'sexual desire' was used in the study, given the lack of systemic absorption of either testosterone or DHEA, sexual motivation is probably a more accurate concept: restored vaginal lubrication, coital comfort, and easier and more intense orgasms could certainly improve motivation.

Conclusion

We do not have evidence of low androgen activity in women with low sexual libido. We do know that scope of measurement is limited. Although we are now able to quantify intracrine testosterone, we cannot measure testosterone production and activity within the central nervous system, which may be more relevant to sexual desire. We also have no information on androgen receptor sensitivity in women with and without sexual dysfunction.

We do not have studies of testosterone supplementation in women with definite sexual disorders, where criteria for diagnosis of disorder are more robust. We do have evidence of modest increase in numbers of sexually rewarding events in women who without any treatment are able to have 2–3 such events per month. The daily dose apparently needs to be 300 μg of testosterone rather than 150 or 450 μg daily to show statistically significant benefit over the placebo.

In North America, testosterone therapy is not approved for women. There are transdermal formulations specifically approved for men, testosterone gels and patches. Dosage is flexible with the former but not the latter (the patches should not be cut). However, there is uncertainty over the amounts absorbed and lack of scientific study of this practice is worrisome.

Long-term risks of testosterone supplementation are basically unknown. Opinion about postmenopausal estrogen therapy changed abruptly in 2002 with the Women's Health Initiative study and changed again far less dramatically in more recent years with widespread realization that women beginning estrogen therapy close to menopause showed benefit rather than harm. Nevertheless, current opinion reflects caution against long-term therapy even for women beginning in early menopause. All of this serves as a warning in the use of systemic sex hormone supplementation for a chronic disorder. Large long-term RCTs of testosterone may prove to show harm rather than benefit in subgroups of women, reminiscent of the situation with estrogen therapy. Moreover, the long-term safety of systemic estrogen is questionable, and the scientific study of testosterone monotherapy to women who already have high testosterone to estrogen ratios is only just beginning.

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Conflicts of interest statement

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