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Transdermal Testosterone For Menopause-Related Hyposexual Desire Disorder: Current Guidelines And Provider Perceptions, Knowledge, And Practice

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TRANSDERMAL TESTOSTERONE FOR MENOPAUSE-RELATED HYPOSEXUAL
DESIRE DISORDER: CURRENT GUIDELINES AND PROVIDER PERCEPTIONS,
KNOWLEDGE, AND PRACTICE

A Thesis Presented

by

Kelly C. White

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The Faculty of the Graduate College

of

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Abstract

Hypoactive sexual desire or low libido in women are collectively referred to as hypoactive sexual desire disorder (HSDD). HSDD is estimated to occur in 10% to 15% of adult women. HSDD is likely the most common female sexual dysfunction (FSD) in menopausal women. The hallmark of the diagnosis is personal distress and interpersonal difficulties resulting from low sex drive. Most women will not seek help for this problem. Studies have suggested that primary care providers and gynecologic healthcare providers report not feeling qualified to treat patients with sexual dysfunction, especially HSDD. Testosterone, specifically transdermal testosterone, has been suggested to play an integral part in the treatment of HSDD in menopause. It is proven to increase the frequency of satisfying sexual activity, sexual desire, and orgasmic response, and to decrease personal distress. Testosterone has a demonstrated safety history and medication tolerance when prescribed for this purpose. In spite of its proven efficacy in relation to HSDD, the Food and Drug Administration (FDA) has not approved testosterone for this purpose, though its use for HSDD is currently suggested by the Endocrine Society in their Clinical Practice Guidelines (CPGs). The primary purpose of this study was to assess Vermont primary care providers' and gynecologic healthcare providers' perceptions, knowledge, and practices regarding treatment of HSDD in naturally induced menopause with a focus on transdermal testosterone. After respondent inclusion criteria and demographic information about the respondents was collected, the study asked questions and tested knowledge about topics regarding menopause and sexuality, evaluation of FSD, and treatment of low libido and diminished sexual desire with a focus on testosterone. The study was a descriptive cross-sectional online survey that was completed electronically on a secure server through the University of Vermont. The conclusions were that providers believe sexuality and sexual satisfaction are quality of life indicators and perceived that maintaining sexual function is important to naturally occurring menopausal women. The majority of providers would prescribe a pharmaceutical treatment for menopausal women seeking to maintain their sexual function, enhance sexual satisfaction, and/or treat symptoms of HSDD as long as there were no contraindications. However, testosterone, a proven treatment for women with complaints of low libido and/or diminished sexual desire, was reportedly underutilized. This may be related to inconsistent screening for FSD in menopause at each comprehensive visit and lack of provider knowledge about testosterone (including safety and efficacy) impacting confidence to prescribe testosterone for this purpose. Further, providers were divided on whether low libido and/or diminished sexual desire in naturally occurring menopause is a medical condition or disorder or a natural part of aging. It is unclear how the aforementioned divisions impact evaluation and treatment.

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...

If not for my lovely clinical nursing preceptors who saw my value and worth and were full of praise, consistent direction, and openness to my learning, I may have not seen this whole thing through. They and the patients I served reflected back to me that I was on the appropriate path.

...

I am also deeply appreciative of Professor O'Meara's willingness to help me and serve as my primary committee member. This impassioned topic would not have come to fruition without her numerous and insightful edits and recommendations. I am also extremely thankful for Professor Buck-Rolland's wisdom, graciousness, and steadiness. Also, I thank Professor Callas' signing on at the eleventh hour and giving me whatever joy could possibly be had involving that subject called statistics. Lastly, many thanks to Erica Berquist.

“The literature of menopause is the saddest, the most awful, and the most medical of all genres. You’re sleepless, you’re anxious, you’re fat, you’re depressed - and the advice is always the same: take more walks, eat some kale, and drink lots of water. It didn’t help.” Sandra Tsing Loh

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Chapter 1: Introduction

Overview

The topic of female sexual health and female sexual dysfunction (FSD) is a challenging one for primary care providers (PCPs) and providers of gynecologic healthcare. Female sexual dysfunction is often overlooked in the primary care setting, even though it may be of great importance to both the patient and her sexual partner(s) (Wright & O'Connor, 2015; Zakhari, 2009). The most prevalent FSD reported is hypoactive sexual desire and/or low libido (Leiblum, Koochaki, Rodenberg, Barton, & Rosen, 2006; West et al., 2008). Hypoactive sexual desire or low libido has been estimated to occur in 10% to 15% of adult women in large population-representative and community-based studies and is likely the most common FSD in menopausal women (Rosen, Connor, et al., 2012).

Hypoactive sexual desire or low libido in women is collectively referred to as hypoactive sexual desire disorder (HSDD) and is defined in the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) and the World Health Organization's (WHO) International Classifications of Disease-10 (ICD-10). The diagnosis hinges on associated personal distress and interpersonal difficulties resulting from low sex drive and not the low drive itself (Nappi et al., 2010; Rosen, Maserejian, et al., 2012). Most women will not seek help for this problem (Lindau et al., 2007; Wright & O'Connor, 2015).

Studies have suggested that PCPs and gynecologic healthcare providers do not feel qualified to treat patients with sexual dysfunction, especially HSDD (Harsh, McGarvey, & Clayton, 2008; Zakhari, 2009). In part, this is thought to be related to

patients' reluctance to discuss problems of HSDD with their providers.

In menopausal women, testosterone and sexual desire are thought to be tightly linked because they both decline with age (Nappi, 2015a). Therefore, testosterone, and specifically transdermal testosterone, has been suggested to play an integral part in the treatment of HSDD in menopause. It has been proven to increase the frequency of satisfying sexual activity, sexual desire, and orgasmic response, and to decrease personal distress, as well as having demonstrated safety history and medication tolerance when prescribed for this purpose (Davis & Braunstein, 2012; Goldstat, Briganti, Tran, Wolfe, & Davis, 2003; Shifren et al., 2006).

In spite of its proven efficacy in relation to HSDD, testosterone is still not approved by the Food and Drug Administration (FDA) for this purpose, though its use for HSDD is currently suggested by the Endocrine Society in their Clinical Practice Guidelines (CPGs) as a treatment for HSDD (Wierman et al., 2014). Primary care providers and gynecologic healthcare providers are in a position to advance sexual medicine for menopausal women through treatment of FSD by utilizing the CPGs in relation to HSDD.

Though sexual dysfunction is common in women, particularly menopausal women, it remains underdiagnosed and undertreated; it may be that FSD represents a "silent epidemic" (Cumming, Mauelshagen, & Parrish, 2010). Primary care providers and gynecologic healthcare providers are in a position to address FSD, particularly HSDD, with evidence-based practice that balances safety with efficacy. In order to do so, the healthcare provider must be aware of their biases, perceptions, and the current CPGs in order to assume a proactive role in the evaluation, diagnosis, and treatment.

Purpose

The primary purpose of this study was to assess PCPs' and gynecologic healthcare providers' perceptions, knowledge, and practices regarding treatment of hypoactive sexual desire or low libido in naturally induced menopause with a focus on transdermal testosterone.

Aim one. Explore whether PCPs and gynecological healthcare providers consider HSDD to be a medical disorder or condition warranting pharmaceutical treatment.

Aim two. Evaluate provider perception of the efficacy and safety profile of transdermal testosterone for the treatment of low libido and diminished sexual desire in menopause as well as practice.

Research Questions

Menopause, Sexuality, and Evaluation of Female Sexual Dysfunction. Do primary care providers and providers of gynecologic healthcare believe sexuality and sexual satisfaction should be quality of life indicators for naturally occurring menopausal women? Do they perceive that maintaining sexual function is important to this patient population? And, do providers consistently screen naturally occurring menopausal women for sexual dysfunction at each comprehensive visit regardless of age, health status, or life circumstances?

Low Libido and Diminished Sexual Desire in Naturally Occurring Menopause. Do primary care providers and providers of gynecologic healthcare consider low libido and/or diminished sexual desire in naturally occurring menopausal women to be a medical condition or disorder, a natural part of aging, or both? Have providers ever prescribed a pharmaceutical treatment for naturally occurring menopausal

women whose chief complaint was low libido and/or diminished sexual desire? In their opinion, does the naturally occurring menopausal woman have to report feeling distressed and/or having interpersonal difficulties related to sexual dysfunction in order to receive pharmaceutical treatment for low libido or diminished sexual desire? Furthermore, would they prescribe a pharmaceutical treatment for a naturally occurring menopausal woman who was otherwise healthy and seeking to maintain her sexual function and enhance sexual satisfaction as long as there are no contraindications?

Testosterone and Hyposexual Desire Disorder. Do primary care providers and providers of gynecologic healthcare feel confident in their knowledge base regarding testosterone used for HSDD and how does knowledge about testosterone impact practice?

Hyposexual Desire Disorder and Clinical practice Guidelines. Lastly, do providers prescribe testosterone for this purpose and have they have reviewed the Endocrine Society's 2014 CPG's regarding androgen therapy for HSDD?

Theoretical Nursing Model Used to Guide Research

The Theory of Unpleasant Symptoms (TOUS) is the nursing model used for the conceptual framework of this study. TOUS was developed by four nurses: Linda Pugh PhD, RNC, FAAN, Elizabeth Lenz PhD, RN, FAAN, Renee Milligan PhD, RNC, WHNP-BC, and Audrey Gift PhD, RN and is a middle range nursing theory developed in 1995 then updated in 1997 (Figure 1). An excerpt from *Middle Range Theory of Nursing* proposed that this theory was developed "to improve the understanding of the symptom experience in various contexts and to provide information useful for designing effective means to prevent, ameliorate, or manage unpleasant symptoms and their negative effects" (McEwen & Wills, 2011, p. 236).

The Theory of Unpleasant Symptoms placed emphasis on the symptom experience with potentially other symptoms occurring concurrently, instead of looking at a single symptom in isolation. The nursing implication is that successful management of one symptom is likely to play a positive role in other symptoms due to the commonalities of the symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Lenz and colleagues (1997) pointed out that TOUS has three main components.

The first component proposes that situational and/or environmental, psychological, and physiological factors are precursor variables or influential factors that have an impact on a patient's predisposition to an unpleasant symptom experience or how the unpleasant symptom is manifested. The environmental and/or situational factors are the components of the physical and social environment that are likely to have an impact on the patient's experience resulting from the symptom. Psychological factors include such components as patient's mood and mental state (depression), the level of knowledge and uncertainty regarding the symptoms including their likely meanings (patient's perception of the symptom experience), and the patient's affective response to the symptom or illness. Physiological factors are mostly linked to symptoms that cause variations in the normal body functioning such as abnormal laboratory results and comorbidities (Lenz et al., 1997).

The second component is the symptom or symptoms that the patient experiences. The dimensions of symptoms include intensity, timing, distress, and quality. Intensity is the amount, strength or severity of the symptom that the patient is experiencing. Timing entails the frequency of the symptom's occurrence, the time duration that the symptom persists, or a combination of both duration and frequency. The distress component of

symptoms is the degree to which a patient is bothered by or reacts to the symptom(s). The quality component of a symptom refers to the descriptors utilized in characterizing the symptom. Additionally, TOUS proposes that multiple symptoms resulting from a single cause can be viewed either alone or in combination (Lenz et al., 1997).

The third component involves the outcomes associated with the symptom experience. According to TOUS, performance is the outcome of symptoms and entails cognitive and functional activities. Functional performance is broadly measured by physical activities, daily living activities, social interaction, and role performance. Cognitive performance entails problem solving, thinking, and concentrating. The TOUS model suggests that performance depends on the nature and level of the experience associated with the symptom (Lenz et al., 1997).

Figure 1. Updated version of the middle-range theory of unpleasant symptoms.

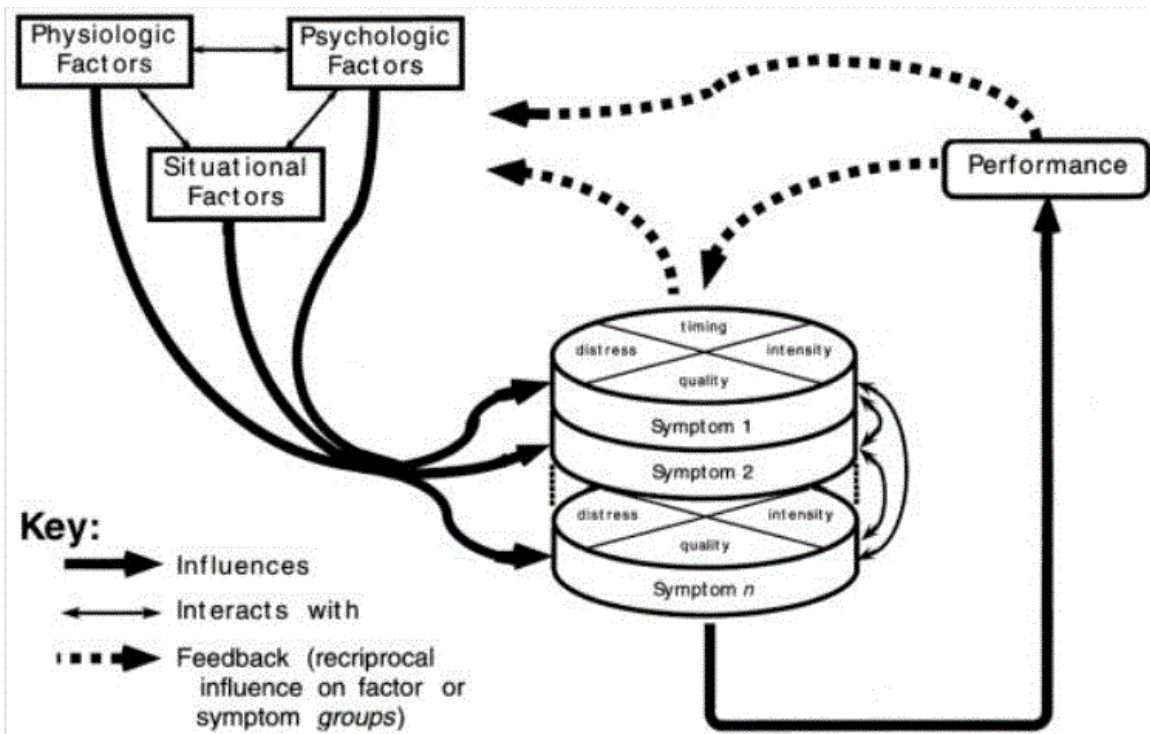


Figure 1. (Lenz et al., 1997).

Hyposexual desire disorder in menopause may be underdiagnosed and undertreated in the primary care setting, in part, due to perceptions that female sexual complaints are thought to be too complex due to the many variables impacting sexuality. TOUS provides a framework for providers to link research with practice and a theory on which to base their management approach for naturally occurring menopausal women who complain of or report decreased sexual desire an/or low libido. In essence, TOUS can help guide the appropriateness of a provider's decision to prescribe testosterone for a patient seeking help with this problem.

The Theory of Unpleasant Symptoms and Nurse Practitioner Competencies

The Theory of Unpleasant Symptoms provides the framework for evidenced-based patient centered care for HSDD as defined by the Nurse Practitioner Core Competencies (2014) and helps “NPs to meet the complex challenges of translating rapidly expanding knowledge into practice and function in a changing health care environment.” Nurse practitioner competencies in conjunction with TOUS can assist with advancing sexual health for women in menopause through: scientific foundation (by critically analyzing data and evidence for improving advanced nurse practice and by translating research and other forms of knowledge to improve practice processes and outcomes), leadership (by guiding change to improve health and by providing leadership in the translation of new knowledge into practice), practice inquiry (by analyzing clinical guidelines for individualized application into practice), and independent practice competencies (by practicing independently and successfully managing previously diagnosed and undiagnosed patients through patient centered care with the patient as a full partner in decision making).

Chapter 2: Literature Review

Background

Female sexual complaints are common. The 1992 National Health and Social Life Survey revealed that some form of sexual dysfunction affects 43% of women with the most common complaints being decreased desire, decreased sexual interest, and low libido among women of all ages, which are mediated in part by declines in testosterone levels and changes in sexual function following menopause (Frank, Mistretta, & Will, 2008; Modelska & Cummings, 2003). In 2005, The Global Study of Sexual Attitudes and Behaviors (GSSAB) found similar results in a larger-scaled international survey of sexual problems among men and women who were 40 to 80 years of age (Feldhaus-Dahir, 2009a). More current research indicates that only about 18% of women with sexual concerns spontaneously volunteer information about sexual dysfunction to their PCP (Wright & O'Connor, 2015).

Low testosterone levels have been associated with loss of libido, decreased sexual activity, diminished feelings of physical wellbeing, and fatigue (Davis & Braunstein, 2012; Goldstat et al., 2003; Kingsberg, 2007). Furthermore, recent data found a significant positive association with testosterone, sexual desire, arousal, and masturbation in midlife women from the United States (US) across the menopausal transition (Nappi, 2015a). In a European cohort of healthy women aged 19-65 years, sexual desire was measured with a validated questionnaire and correlated overall with free testosterone (Nappi, 2015a). Nappi (2015a) concluded that the data from the aforementioned studies support the therapeutic use of testosterone for HSDD when low testosterone levels are assessed.

Satisfaction with one's sex life has been considered a major quality of life indicator; however, evaluation, diagnosis, and management of FSD has been largely overlooked by the healthcare community, especially in primary care (Krapf & Simon, 2009; Zakhari, 2009). This has been attributed by some to a gender gap in the development of sexual medicine, where the medical field has long accepted the importance of male sexuality but sexual dysfunction in women and treatment options to address these concerns have been met with controversy or a lack of acknowledgement (Nappi, 2015b).

Female sexual dysfunction defined. Historically, the DSM-4-TR divided FSD into four categories: sexual desire, sexual arousal, orgasmic, or sexual pain disorders (Frank et al., 2008). Hence, FSD has been traditionally defined as a persistent or a recurrent reduction of sex drive, or an aversion to sexual activity, difficulty becoming aroused, an inability to reach orgasm, or pain during sexual intercourse (Frank et al., 2008; Modelska & Cummings, 2003). In 2004, the Second International Consensus of Sexual Medicine accepted revised definitions of FSD in that symptoms for sexual dysfunction must also cause distress (Frank et al., 2008). In summary, to meet the criteria for FSD, the symptoms must be recurrent, persistent, and must also cause personal distress and/or interpersonal difficulty (Nappi et al., 2010; Rosen, Maserejian, et al., 2012).

The DSM-5-TR diagnostic criteria combined desire and arousal disorders into female sexual interest/arousal disorder and sexual pain disorders into genito-pelvic pain/penetration disorder (Nappi, 2015b). It also established additional criteria to characterize FSD, such as personal distress to diagnose female sexual interest/arousal

disorder (Nappi, 2015b). Nevertheless, FSD continues to be considered a complex and poorly understood condition that affects women of all ages. It is therefore considered difficult to diagnose and to treat (Frank et al., 2008; Modelska & Cummings, 2003; Nappi et al., 2010). The body of literature regarding low libido in women continues to refer to the problem as HSDD, rather than female sexual interest arousal disorder. Thus, HSDD will be the term used for the purpose and intent of this paper.

Menopause and sexuality. For myriad reasons, menopause has been associated with sexual dysfunction. In part, this is thought to be related to hormonal and physiologic decline due to fluctuating steroid hormone levels that adversely affect the elasticity of the vaginal mucosa and vaginal secretions resulting in vaginal atrophy and pain with sexual intercourse (Thornton, Chervenak, & Neal-Perry, 2015). Menopause is a time marked by social change as well. Social conditions or life stressors, such as divorce, lack of partner, job loss, or declining health are thought to affect the desire for sexuality, however sexuality is expressed (Thornton et al., 2015).

In an attempt to understand the prevalence of sexual activity, behaviors, and problems of older people, a national probability sample of 3,005 US adults 57 to 85 years of age comprising of 1,550 female participants were interviewed to describe the association between sexuality, age, and health status. In this study, Lindau et al. (2007, p. 3) defined sexual activity as “any mutually voluntary activity with another person that involves sexual contact, whether or not intercourse or orgasm occurs.” Sexually active respondents were asked about the presence of sexual problems involving interest, arousal, orgasm, pain, and satisfaction. Questions were also asked about the duration of the

sexual problem, the degree to which it occurred, and about their overall health (Lindau et al., 2007).

The study by Lindau et al. (2007) showed that the prevalence of sexual activity declined with age (73% in the 57 to 64 years age group, 53% in the 65 to 74 years group, and 26% in the 75 to 85 years group were sexually active). Women were significantly less likely than men to report sexual activity, and approximately half of both men and women reported at least one bothersome sexual problem. The most prevalent sexual problem reported among older women was low desire (43%). Yet, only 22% of the women in this study reported having discussed sex with a physician since the age of 50 years (Lindau et al., 2007).

The study by Lindau et al. (2007) was similar to the findings from the 1990 Women's Healthy Aging Project (WHAP) cohort, which was a prospective, longitudinal, epidemiological study of 438 Australian women that spanned two decades. The study was also an extension of the Melbourne Women's Midlife Health Project, where a significant decline from 74% to 56% in sexual activity was reported between early postmenopausal women and late postmenopausal women (Thornton et al., 2015). This study concluded that the most important factors influencing middle-aged women's sexual functioning were the previous level of sexual functioning, changes in partner status (gaining a new partner has a very positive effect, whereas losing a partner has a negative effect), feelings for a partner, and the menopausal decline in sexual functioning, which is related to the decline in estradiol and testosterone affecting sexual interest, arousal, enjoyment, orgasm, and lastly dyspareunia (Cumming et al., 2010).

A cross-sectional analysis of 2012/13 and a longitudinal analysis from 2002/04 of the population based Australian cohort of the WHAP applied validated instruments such as the Short Personal Experience Questionnaire (SPEQ), Female Sexual Distress Scale (FSDS), Hospital Anxiety and Depression Scale, and the Geriatric Depression Scale to describe the change in sexual functioning of women from early menopause to late menopause. Two-hundred and thirty women responded, with the mean age of 70 years. The study concluded that in late menopause, approximately half of the women were still sexually active and the most important predictors were partner availability and no history of depression (Lonnee-Hoffmann, Dennerstein, Lehert, & Szoeki, 2014).

Paradoxically, being sexually active or having a sexually available partner in menopause was associated with higher levels of personal distress (Lonnee-Hoffmann et al., 2014). The authors suggested that among naturally menopausal sexually active women with a partner, increasing sexual distress might be related to concerns about declining sexual interest and activity and the effect this has on the relationship especially if there is discordance in sexual needs between the partners (Lonnee-Hoffmann et al., 2014).

Significance

For several decades, sex has been recognized as a quality of life indicator (Nappi, 2015b; Wylie et al., 2010; Zakhari, 2009). Female sexual dysfunction, and in particular HSDD, correlates with an increased prevalence of low physical and emotional satisfaction, poor self-image, and unhappiness (Nappi, Wawra, & Schmitt, 2006; Thornton et al., 2015). Nappi et al. (2010, p. 168) wrote, “The negative personal issues associated with decreased sexual interest include feeling less feminine, feeling like a

sexual failure, low self-esteem, insecurity, inadequacy, and letting a partner down.”

Additionally, the distress has been positively associated with depression and it is particularly evident when a current partner is present (Nappi et al., 2010).

Thornton et al. (2015) surmised that increased life expectancy for women brought about by improved access to medical care and nutrition have raised women’s expectations for a healthier longer life, and included in life quality is maintaining sexual function and enjoyment. Additionally, with the FDA approval of phosphodiesterase type 5 inhibitors for male erectile dysfunction, it has been proposed that there are now more menopausal women with male partners who have renewed sexual interest and improved function, which contributes to the prevalence of FSD and HSDD being that available sexual partners’ desires increase personal distress and/or interpersonal difficulty (Thornton et al., 2015).

Regardless of age and menopausal status, sexual interest and the importance of sexuality continues for many women, regardless of declining sexual activity and function (Lindau et al., 2007; Thornton et al., 2015). Seventy-six percent of 3,302 middle-aged multi-ethnic women in the 2003 Study of Women’s Health Across the Nation (SWAN) reported that sex was moderately or extremely important to them (Thornton et al., 2015). In an online questionnaire offered on an independent United Kingdom (UK) menopause website, there were 1002 female responses to a sexual questionnaire, which was patient-tailored and clinician-led (Cumming, Herald, Moncur, Currie, & Lee, 2007). Of the postmenopausal respondents, 88% reported that an active sex life was important to them as well (Cumming et al., 2007).

Unfortunately, studies have suggested a lack of awareness of the importance of sex to patients on the part of PCPs, especially in older, menopausal women (Abdolrasulnia et al., 2010; Harsh et al., 2008). The reluctance to enquire about sexual symptoms leads to an incomplete assessment of sexual function, activity, and satisfaction. Therefore, this reluctance has been shown to lead to a failure to legitimize the needs and requests of patients who desire a healthy and satisfying sex life (Abdolrasulnia et al., 2010; Wylie et al., 2010).

Findings from large population based studies, such as the Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) and the Women's International Study of Health and Sexuality (WISHeS), clearly indicate that FSD is a burden for many women, which poses myriad problems and subsequent personal distress and interpersonal difficulty (Leiblum et al., 2006; Thornton et al., 2015). These studies concluded that a menopause-related decrease in sexual desire and low-libido can be extreme and even debilitating (Cappelletti & Wallen, 2015; Leiblum et al., 2006; Thornton et al., 2015).

Hypoactive Sexual Desire Disorder in Menopause

Though HSDD has been the most prevalent sexual disorder reported by women of all ages from multiple studies in the US and Europe, it is considered a FSD particularly common among menopausal women either through natural menopause or surgically induced menopause (Leiblum et al., 2006; Rosen, Maserejian, et al., 2012; West et al., 2008). The risk of HSDD is greatest in the surgically induced menopause group and is thought to be related to the abrupt reductions in circulating estradiol and testosterone levels (Thornton et al., 2015). A US study published 2009 showed that at least 16 million

women over the age of 50 experience low sexual desire, with approximately four million meeting the criteria for HSDD (Krapf & Simon, 2009).

Definition. Specifically, HSDD is defined by absent/reduced interest or thoughts/fantasies in sexual activity, or reduced/no initiation of sexual activity, unreceptiveness to a partner's initiatives, or absent/reduced sexual excitement or pleasure during sexuality activity that results in personal distress or interpersonal difficulty with no other iatrogenic or organic cause for the sexual dysfunction. The clinical features must occur for at least six months (Thornton et al., 2015). HSDD is not considered to be nor should be confused with an aversion to sex (Frank et al., 2008; Wright & O'Connor, 2015).

Generalized acquired HSDD has been the most common diagnosis when the condition is not dependent on a specific situation or relationship and has developed after a period in which sexual desire and sexual functioning were considered normal (Nappi et al., 2010). The diagnosis may be comorbid with another sexual dysfunction, but it cannot be exclusively attributed to another medical condition or to the physiological effects of a medication (Nappi et al., 2010). Hence, lack of sexual desire in menopausal women does not necessarily mean that they have a sexual dysfunction. For some menopausal women, sexual expression ceases to become an important part of their life and is not associated with interpersonal distress or interpersonal difficulties and therefore, the diagnosis of HSDD does not apply.

Prevalence. Desire difficulty has been the most common FSD experienced by women of all ages, but particularly in either natural or surgically induced menopause. There have been many prevalence studies that have investigated HSDD as a FSD.

To determine the prevalence of HSDD among US women by reproductive status and age and to explore the correlates of sexually related distress, the WISHeS questionnaire was mailed to a national sample of US women in 2000. The survey included validated questionnaires: The Short Form-36, which measured the overall health status; the Profile of Female Sexual Function (PFSF), which assessed sexual desire; and the Personal Distress (PD) Scale, which measured distress caused by low desire. Four groups of women were studied: surgically postmenopausal, aged 20 to 49 years and 50 to 70 years; premenopausal, aged 20 to 49 years; and naturally postmenopausal, aged 50 to 70 years. Clinically derived cutoff PFSF and PD Scale scores were used to classify women with HSDD and to determine its prevalence. The relations between sexual desire and frequency of sexual activity or relationship satisfaction were then assessed, and the overall health status of HSDD women and women with normal desire were compared. WISHeS found that up to nine percent of natural and 26% of surgically postmenopausal women suffer from a persistent and distressing lack of sexual desire (Leiblum et al., 2006).

In another cross-sectional study of US women from 2004-2005, the prevalence of low sexual desire and HSDD was estimated with a focus on menopausal status. From a probability sample of US households, 2207 US women aged 30 to 70 years old and in stable relationships were interviewed by telephone. The analysis focused on 755 premenopausal women, 552 naturally menopausal women, and 637 surgically menopausal women. Hyposexual desire disorder was defined using the PFSF and the PD Scale. Prevalence of low sexual desire ranged from 26.7% among premenopausal women to 52.4% among naturally menopausal women (West et al., 2008).

In 2004, the aforementioned study of Lindau et al. (2007) examined the prevalence of sexual activity, behaviors, and problems among a nationally representative probability sample of 3005 (1550 women and 1455 men) US citizens 57 to 85 years of age from households across the US. The most prevalent sexual problem found among women was low desire (43%) (Lindau et al., 2007).

Hayes et al. (2006) calculated the prevalence of sexual difficulty/dysfunction (desire, arousal, orgasm, and pain) using data from 11 published studies. They found low sexual desire among 64% of participants (range 16–75%) orgasmic difficulties among 35% of women (range 16–48%), arousal problems among 31% (range 12–64%) and pain that interfered with intercourse among 26% (range 7–28%) (Hayes, Bennett, Fairley, & Dennerstein, 2006; Hayes et al., 2007). Desire was the most common sexual difficulty among women (Hayes et al., 2006; Hayes et al., 2007). However, there was not additional data that established whether or not this caused distress (Hayes et al., 2006; Hayes et al., 2007).

The first in-person diagnostic interview study published in 2012 aimed to determine the prevalence of generalized acquired HSDD in women aged 18 years or older who attended primary care clinics or obstetrics and gynecology clinics for non-urgent visits. In 2010 a total of 701 women were enrolled at 20 clinical sites across the US. A completed two-part, self-administered questionnaire as well as a validated, structured, in- person diagnostic interview conducted by a trained health professional was used for diagnosing HSDD according to DSM-4-TR criteria. In this sample an overall prevalence of acquired generalized HSDD rate was observed in 7.4% of the population

with a marked increase in prevalence in midlife women 40 to 59 years old (Rosen, Connor, et al., 2012).

The PRESIDE survey of more than 31,000 women over 18 years of age in the US documented sexual distress symptoms including HSDD, which was the most commonly reported FSD and peaked in middle-aged women. Between 18 to 44 years of age the prevalence of HSDD was 8.9%, while it was 12.3% between 45 to 64 years and 7.4 % in women 65 years or older (Thornton et al., 2015). Overall, HSDD was 20% higher in postmenopausal than in premenopausal women (Nappi et al., 2010; Thornton et al., 2015).

Characteristics of menopausal women with HSDD. A large multicenter patient registry was established in accordance with current guidelines to provide a comprehensive, longitudinal assessment of the clinical profile of women with acquired generalized HSDD, including both premenopausal and menopausal women receiving care in 33 US clinical sites and settings. Recruitment was completed in August 2010. The goal of the study was to provide the first comprehensive and in-depth profile of a large, diverse sample of women with acquired generalized HSDD by systematically comparing the clinical presentation, sexual and relationship characteristics, and care seeking experiences. Data was analyzed from a sample of 1,574 women enrolled in the HSDD Registry cohort (Rosen, Maserejian, et al., 2012).

The results of the study demonstrated that the participants were predominately married or living with a partner (81.7%) and represented a range of racial and ethnic backgrounds. Most described their HSDD severity as “moderate to severe,” with 26.5% rating the problem severe. Less than half of the overall sample had sought professional

help, among whom hormonal treatments had been used by only 23.7% of postmenopausal women and by 7.6% of the premenopausal women. Interestingly, most women (69.8%) reported being happy in their relationship and 61.8% were satisfied with their partner's communication (Rosen, Maserejian et al., 2012). The conclusions of the study were that most of the women with HSDD were in long-term partner relationships with high levels of overall relationship satisfaction.

Hyposexual desire disorder, a problematic diagnosis. Some researchers feel that HSDD is a problematic diagnosis because there is no scientifically established norm for sexual activity, feelings, or desire (Meixel, Yanchar, & Fugh-Berman, 2015). It has been suggested the HSDD is a typical example of a condition that was sponsored by the pharmaceutical industry to prepare the market for a specific treatment such as with transdermal testosterone and Flibanserin (Meixel et al., 2015). This is what Tiefer (2006) referred to as FSD "disease mongering." Meixel et al. (2015, p. 859) asserted that HSDD may be a form of "disease branding" or "condition branding" as a marketing technique in which a company adopts or invents a condition and then develops the so-called disease state prior to marketing pharmacological treatments for that condition. The three strategies outlined by Meixel et al. (2015) to foster the creation of a condition and aligning it with a product (most likely pharmaceutical) are: elevating the importance of an existing condition, redefining an existing condition to reduce a stigma, and developing a new condition to build recognition for an unmet market need.

Meixel et al. (2015) argued that HSDD is a typical example of the medicalization of a natural state, adding that HSDD was established by the industry in 2004 to prepare the market for a testosterone patch for women. Moynihan (2005) asserted that it was

Robert Wilson's bestselling book *Feminine Forever* that contributed to the notion the menopause was a disease of hormone deficiency, to be cured with hormone replacement which was discovered to have done more harm than good though this was primarily related to unopposed estrogen administration.

Nevertheless, sexuality is considered a key aspect of women's physical and psychological health potentially throughout the entire lifespan (Sobecki, Curlin, Rasinski, & Lindau, 2012). The contribution of John E. Buster, M.D. "Managing female sexual dysfunction," emphasized HSDD as a driving disorder at the heart of all other FSDs; in that he hypothesized that nothing happens without sexual desire (Buster, 2013). He added that successful resolution of HSDD frequently facilitates resolution of other disorders. Buster (2013) argued that central to understanding HSDD is the impact of the aging female sexual endocrinology and its effects on both prevalence and expression patterns of sexuality and FSD.

General management of HSDD. Hyposexual desire disorder is often considered a sexual dysfunction that is difficult to treat due to the large number of potential causes and contributing factors (Abdolrasulnia et al., 2010). Nappi et al. (2010) recommended a balanced approach comprising both biological and psycho-relational factors. The North American Menopause Society (NAMS) recommended that PCPs ask women of midlife age about sexual concerns at every comprehensive visit (Shifren & Gass, 2014). Zakhari (2009) emphasized that, as with any condition a complete history and physical examination are essential to identify the etiology of the problem reported.

Specifically, for problems of hypoactive sexual desire and/or low libido, both NAMS and the American Congress of Obstetricians and Gynecologists (ACOG) have

established recommendations for the treatment of underlying depression and anxiety as well as adjustment of antidepressant medications. Other recommendations for the management of HSDD include examination of the problem in relation to an adverse situation or chronic disease such as depression, gynecological disorders, and/or the use of certain medications such as antidepressants, oral contraceptives, or corticosteroids (American Congress of Obstetricians and Gynecologists, 2012; Frank et al., 2008; Shifren & Gass, 2014). The role of long-term medical diseases, especially gynecologic diseases, and minor ailments, medications, and psychosocial difficulties, including prior physical or sexual abuse, are etiologic factors that must be scrutinized (Nappi et al., 2010).

Counseling and sex therapy, with a focus on identifying sexual technique, increasing sexual novelty, and enhancing the partner relationship and communication are effective interventions for many individuals and couples with sexual problems (Abdolrasulnia et al., 2010; Rosen, Connor, et al., 2012). In addition, identification and treatment of substance abuse, as well as the underlying factors that precipitated it, often result in improved sexuality and overall quality of life. At the very least, it is suggested that the provider must provide patient education and reassurance, and make appropriate referrals when indicated (Frank et al., 2008).

Current clinical guidelines for treatment of HSDD with androgen therapy.

The complexity of factors involved in HSDD and poor awareness that low desire associated with distress is considered a medical condition slowed down the development of drugs specifically designed for women with FSD (Nappi, 2015b). Though various randomized placebo-controlled trials have demonstrated efficacy and safety, the FDA has

not approved hormonal pharmacotherapy for HSDD (Nappi, 2015b). Flibanserin (Addyi), a 5-HT_{1A} receptor agonist, is currently the only pharmaceutical approved by the FDA for low sex drive in women and was made available late in 2015.

Though there is currently no FDA approved hormonal treatments for menopausal women with HSDD, transdermal testosterone is considered an effective short-term therapy; however, there is little evidence to support long-term use (longer than six months) (Wierman et al., 2014).

In 2014, the Endocrine Society updated its 2006 CPGs regarding androgen therapy (testosterone and dehydroepiandrosterone) in women for treatment of HSDD after appointing a task force consisting of the Endocrine Society, ACOG, American Society for Reproductive Medicine (ASRM), European Society of Endocrinology (ESE), and the International Menopause Society (IMS) consisting of six experts, a methodologist, and a medical writer. The guidelines were published in the 2014 CPGs entitled "Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline," in the *Journal of Clinical Endocrinology and Metabolism* (JCEM), a publication of the Endocrine Society (Wierman et al., 2014).

The Society updated its 2006 recommendations to address new research concerning therapy in women as well as advances in testosterone testing and measurement techniques. The Task Force commissioned two systematic reviews of published data and considered several other existing meta-analyses and trials (Wierman et al., 2014). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was used; the strength of a recommendation was indicated by a number "1" which indicated that the recommendation was strong or by a

“2”, which was considered to be a weak recommendation that is suggested (Wierman et al., 2014).

In regards to the 2014 CPGs, the only situation where the Endocrine Society suggested prescribing testosterone therapy for women was if she was diagnosed with HSDD. Testosterone therapy remained contraindicated in women with breast or uterine cancer and cardiovascular or liver disease (Nappi et al., 2010; Wierman et al., 2014). In cases of HSDD without contraindications, the CPGs suggested a three-to six-month trial of testosterone to see if the therapy improved sexual function, but recommended against testosterone therapy in “otherwise healthy women” (Wierman et al., 2014). Hence, transdermal testosterone therapy for HSDD is a GRADE 2 recommendation according to the Endocrine Society’s CPGs.

Though monitoring androgen levels before or during treatment had not proven to be useful due to the inability to measure total and free testosterone in women accurately and precisely using currently available assays, the Endocrine Society’s 2014 guidelines have suggested measuring testosterone levels at baseline and after three to six weeks of initial treatment to assess patient overuse (Krapf & Simon, 2009; Wierman et al., 2014). The 2014 CPGs suggested cessation of therapy for women who have not responded within six months of treatment and the point was made that there was no safety and efficacy data for testosterone therapy after use for 24 months (Wierman et al., 2014).

Testosterone and HSDD

Testosterone has been used for more than six decades for various female disorders (Cappelletti & Wallen, 2015). Though transdermal testosterone is an effective short-term treatment for HSDD in women, the FDA has not approved it for this use. Nevertheless,

testosterone is currently prescribed as an off-label treatment for hypoactive sexual desire and/or low libido and its use is currently suggested by the Endocrine Society's 2014 CPGs for this sexual dysfunction (Cappelletti & Wallen, 2015; Wierman et al., 2014).

Testosterone is thought to contribute to initiation of sexual activity, receptivity, and permission for sexual behavior (Feldhaus-Dahir, 2009a; Hollingsworth & Berman, 2006; Nappi et al., 2003; Wylie et al., 2010). There is also thought that testosterone can modulate the clitoral and vaginal physiology by facilitating vaginal smooth muscle relaxation, enhancing lubrication, engorgement, and sensation in part by conversion to estradiol (Feldhaus-Dahir, 2009a; Hollingsworth & Berman, 2006; Sherwin & Gelfand, 1987; Traish, Kim, Min, Munarriz, & Goldstein, 2002).

Androgens and FSD. Low androgen levels are associated with significant deterioration of libido and sexuality in menopausal women. Many studies have demonstrated that sexual desire, function, and activity increase with androgen supplementation. This is particularly true of testosterone, a sex steroid considered to be the most clinically relevant circulating androgen (Feldhaus-Dahir, 2009b; Hollingsworth & Berman, 2006; Randolph et al., 2015). Therefore, the decline of androgen levels through natural or surgically induced menopause has led to the hypothesis that decreased testosterone is related to diminished desire (Krapf & Simon, 2009).

Though low circulating levels of androgens such as testosterone are associated with low sexual desire, the results of numerous studies addressing this are contradictory and no level of a single androgen is predictive of sexual dysfunction in women (Randolph et al., 2015; Wylie et al., 2010). In fact, the Endocrine Society recommends against making a clinical diagnosis of androgen deficiency syndrome in healthy women due to

the lack of a well-defined syndrome, and the lack of data correlating androgen levels with specific signs and symptoms (Wierman et al., 2014). Furthermore, the link between androgen levels and sexual dysfunction has been muddied by the inability to measure total and free testosterone levels in women accurately and precisely using the current available assays and many women tested are already taking hormonal treatments (Krapf & Simon, 2009; Nappi, 2015b). Therefore, the measurement of total testosterone or free testosterone to diagnose androgen deficiency in clinical practice has not been typically utilized (Nappi, 2015b).

Nevertheless, recent data measuring total testosterone levels found a significant positive association with sexual desire, arousal, and masturbation in midlife US women across the menopausal transition (Nappi, 2015a). Furthermore, in a European cohort of healthy women aged 19 to 65 years, sexual desire, measured with a validated questionnaire, correlated overall with free testosterone (Nappi, 2015a). Nappi (2015a) concluded that the data from the aforementioned studies support the therapeutic use of testosterone for low desire and sexual dysfunction in clinical conditions in which androgen deficiency may be accurately diagnosed though it is not typically utilized in clinical practice to make the diagnosis of HSDD.

Testosterone defined. Testosterone, a sex steroid, is synthesized from cholesterol in the ovaries and the adrenal glands and from the conversion of circulating androgens in the peripheral tissues (Feldhaus-Dahir, 2009a; Hollingsworth & Berman, 2006; Krapf & Simon, 2009). Total and free testosterone levels decline with age in premenopausal women such that women in their 40s and 50s have half the circulating levels of women in their 20s, after which the levels then remain stable across the

menopausal transition where no further decrease is observed (Goldstat et al., 2003; Shifren et al., 2006). Decreases of testosterone in women are thought to decrease gradually due to the aging process and declining ovarian and adrenal function (Krapf & Simon, 2009).

Testosterone is the most abundant active sex steroid in women throughout the female lifespan and is measured in 10-fold higher units than estradiol (R. Glaser & C. Dimitrakakis, 2013). Additionally, there are exponentially higher levels of proandrogens: dihydroepiandrosterone sulfate (DHEAS), dihydroepiandrosterone (DHEA) and androstenedione that supply significant amounts of testosterone to the androgen receptor similarly in both sexes (R. Glaser & C. Dimitrakakis, 2013).

Testosterone, a history. Following the isolation and synthesis of testosterone in 1935, physicians began prescribing testosterone therapy for a wide range of medical conditions in both men and women (Cappelletti & Wallen, 2015). However, androgen therapy has been used in women since the early 1900s (Feldhaus-Dahir, 2009b). In women, testosterone was frequently administered for treatment of menstrual complaints and as a tumor suppressant in cases of advanced breast cancer.

In 1974, the FDA approved testosterone for female metastatic breast cancer (Feldhaus-Dahir, 2009b). Early researchers anecdotally reported that some women treated with high-dose testosterone therapies mentioned an unexpected increase in sexual desire (Cappelletti & Wallen, 2015). These women received high doses of testosterone (75-350 mg/week) that produced somatic virilization, such as lowering of the voice, clitoral enlargement, and the growth of unwanted facial hair. In response to these initial studies the amount of testosterone was decreased to 20-75 mg/week to increase sexual

desire in female participants. The conclusions were that testosterone increased sexual desire in all the participants, but that when it was combined with estrogen it was more effective than when taken alone. Of note, there are no documented placebo controls from this time period (Cappelletti & Wallen, 2015).

In 1983, one of the first randomized controlled trials of exogenous estrogen in postmenopausal women was conducted with testosterone, which was added to an estrogen implant in 40 menopausal women with decreased sexual interest (Dow, Hart, & Forrest, 1983). No significant differences were found between the groups. However, in the first study that included a testosterone alone arm, Sherwin et al. (1985) conducted a prospective crossover study examining the effect of intramuscular testosterone on sexual function in 53 surgically menopausal women. In this study, participants were randomized to testosterone alone, estrogen alone, testosterone plus estrogen, or a placebo. Significant improvements in libido and sexual pleasure were noted in the testosterone treated group (Sherwin, Gelfand, & Brender, 1985). Davis et al. (1995) conducted a similar study where testosterone was added to estrogen implants. Again women receiving the testosterone showed significant improvements in sexual activity, satisfaction, pleasure, and frequency of orgasm in comparison to the estrogen group (Davis, McCloud, Strauss, & Burger, 1995).

A double-blinded trial in 1998 examined the efficacy of oral testosterone therapy in postmenopausal women already using estrogen therapy (Sarrel, Dobay, & Wiita, 1998). The women were randomized into two groups: oral esterified estrogens or esterified estrogens plus oral methyltestosterone. At eight weeks, the women receiving testosterone therapy reported significant improvements in sexual desire and satisfaction

(Sarrel et al., 1998). The largest trial incorporating oral testosterone included 218 menopausal women receiving a baseline estrogen therapy with HSDD (Lobo, Rosen, Yang, Block, & Van Der Hoop, 2003). This randomized, double blind trial had a four-month treatment period with estrogen or estrogen combined with testosterone. Testosterone recipients reported increased sexual desire and interest, but no improvements in sexual function (Lobo et al., 2003). Then in 2004, a Cochrane database systematic review reconfirmed that testosterone improved libido, sexual function, and sexual activity (Somboonporn, Davis, Seif, & Bell, 2005).

Hence, while earlier studies established that oral and implantable testosterone therapy improved sexual desire and activity in both natural and surgically induced menopausal women, research for other routes of administration continued. Transdermal testosterone in the form of patches and gels were discovered to have the advantage of avoiding first-pass hepatic metabolism. This spawned many studies of the effects of transdermal testosterone on a menopausal sexual desire continued (Krapf & Simon, 2009).

Intrinsa. In 2004, the FDA reviewed clinical trial data for Intrinsa, a transdermal testosterone patch manufactured by Proctor and Gamble for the treatment of HSDD in postmenopausal women. The FDA voted in favor of Intrinsa 14 to three based on the effectiveness in treating women with HSDD; however, it was not approved because the FDA felt that the 18-month clinical trial was lacking for long-term safety data (Feldhaus-Dahir, 2009a).

Impact of the Women's Health Initiative. Feldhaus-Dahir (2009) suggested that medical professionals believed that the FDA was apprehensive to approve transdermal

testosterone due to the results of the 2002 Woman's Health Initiative (WHI), which showed that treatment with estrogen and progestin caused breast cancer (Shufelt & Braunstein, 2009). Since testosterone is considered to be by some a prohormone for estradiol, testosterone use in women raised concerns that conversions to estrogen at the local tissue level may be deleterious, especially with cardiovascular, breast, and endometrial health (Feldhaus-Dahir, 2009b). Since then, all forms of hormone therapy in menopausal women have come into question and under close scrutiny (Feldhaus-Dahir, 2009b).

Testosterone and antidepressant treatment-emergent loss of libido. Female sexual dysfunction is a side effect of selective serotonin and noradrenalin reuptake inhibitor therapy (SSRI/SNRI). A double-blind, randomized, placebo-controlled study was conducted on 44 women aged 35 to 55 years who were on a stable dose of SSRI or SNRI with treatment-emergent loss of libido. The women were randomly allocated to treatment with a transdermal testosterone patch delivering 300 mcg of testosterone/day or an identical placebo patch for 12 weeks. The primary outcome measure was the change in the Sabbatsberg Sexual Self-Rating Scale (SSS) total score over 12 weeks. The four-week frequency of Satisfactory Sexual Events (SSEs) and the Female Sexual Distress Scale-Revised (FSDS-R) were also measured (Fooladi et al., 2014).

The mean total serum testosterone level at 12 weeks in the transdermal group was 2.1 nmol/L. The increase in the four-week frequency of SSEs was significantly greater for the transdermal testosterone group than the placebo group (an increase of 2.3 events vs. 0.1), though the change in the SSS score did not differ between the two groups and the between-group difference in the change in the FSDS-R score only approached

statistical significance. No women withdrew because of androgenic adverse events. It was concluded that transdermal testosterone therapy resulted in a significant increase in the number of SSEs in comparison to the placebo therapy in women with SSRI/SNRI emergent loss of libido. This study provided the first evidence that transdermal testosterone therapy may be a treatment option for women with SSRI/SNRI emergent loss of libido who need to remain on their antidepressant therapy (Fooladi et al., 2014).

Studies that evaluate the safety and efficacy of transdermal testosterone.

Based on presentations at a satellite symposium during the 2011 annual meeting of the International Society for the Study of Women's Sexual Health, it was determined that transdermal testosterone is considered an effective and safe therapy for menopausal women with HSDD. The safety and efficacy were demonstrated with and without concomitant estrogen or estrogen/progestin therapy based on randomized, double-blind, placebo controlled studies. Furthermore, interim data from a long-term phase three-safety trial of a testosterone gel has continued to demonstrate a low rate of cardiovascular events and breast cancer in postmenopausal women at an increased cardiovascular risk (Davis & Braunstein, 2012).

Phase three trials. To investigate the efficacy and safety of transdermal testosterone, two concurrent phase-three trials were conducted in the US, Canada, and Australia. These two large, double-blind multicenter trials are known as the Investigation of Natural Testosterone in Menopausal Women Also Taking Estrogen in Surgically Menopausal Women (INTIMATE SM) 1 and 2 and specifically investigated the safety of a 300-mcg/day-testosterone patch for HSDD in surgically induced menopausal women who are taking transdermal or oral estrogen (Davis & Braunstein, 2012; Krapf & Simon,

2009; Shifren et al., 2006). Taken together, the findings supported the efficacy of the 300-mcg/day-testosterone patch for low sexual functioning women who report low stressful sexual desire after a bilateral salpingo-oophorectomy and hysterectomy and are using estrogen therapy (Krapf & Simon, 2009).

Both trials were 32 weeks in duration, consisting of an eight-week pre-treatment baseline period and a 24-week randomized double-blind placebo controlled treatment period. Patients in both trials had undergone bilateral salpingo-oophorectomy and a hysterectomy at least six months previously and were receiving estrogen therapy. All women were in monogamous relationships with a sexually functioning partner and reported a meaningful loss of sexual desire that was causing them concern (Kingsberg, 2007). Women with sexual dysfunction such as dyspareunia or who were taking medications known to cause sexual dysfunction such as selective serotonin reuptake inhibitors were excluded from the study. A key feature of the trials was the use of a validated study instruments to measure sexual function. The primary efficacy measure was the change in the frequency of total satisfying sexual activity over 24 weeks assessed by the Sexual Activity Log (SAL), which is described as a weekly diary that assessed sexual activity, satisfying sexual events, and number of orgasms over the proceeding seven days. Secondary efficacy measures included changes in the Profile of Female Sexual Function (PFSF). Additionally, the subject's distress related to lack of interest in sex was measured with the Personal Distress Scale (PDS). Both studies concluded that transdermal testosterone treatment for HSDD is effective in surgically menopausal women taking estrogen (Kingsberg, 2007).

Furthermore, the INTIMATE SM 1 and 2 studies both showed a similar adverse event profile. In both studies, the most commonly reported adverse events were skin reactions at the site, which occurred in 30-40% of the participants (Kingsberg, 2007). Androgenic adverse events, such as acne, alopecia, or voice deepening tended to be more common in testosterone treated patients than in the placebo group in INTIMATE SM 2, but not INTIMATE SM 1. The androgenic adverse events were not considered to be significant for 85% of the participants stated that they would continue treatment.

Due to the concerns about the safety and efficacy of testosterone without concurrent estrogen therapy on low sexual desire and libido in postmenopausal women, the phase three Research Study of Female Sexual Dysfunction in Women on Testosterone Patch without Estrogen (APHRODITE) study attempted to address this lack in the research and is so far the longest trial to date, spanning 52 weeks (Krapf & Simon, 2009).

Though menopausal women with HSDD experienced statistically significant improvements in the frequency of satisfying sexual activity, sexual desire, and distress with testosterone treatment in phase three trials it was not known if the magnitude of the effects were clinically meaningful. Therefore, a representative sample of two randomized placebo-controlled trials (N=1094) were interviewed before un-blinding at the end of the study to assess the efficacy and safety of 300 mcg/day of transdermal testosterone. Women were asked, "Overall, would you say that you experienced a meaningful benefit from the study patches?" Fifty-two percent of the women receiving a testosterone patch experienced a meaningful treatment benefit in comparison to the 31% who received placebo. Therefore, the conclusions were that surgically menopausal women with HSDD received clinically meaningful benefits (Kingsberg et al., 2007).

INTIMATE NM1. This study was the first large, multicenter, randomized, double-blind, placebo-controlled parallel group trial to evaluate the safety and efficacy of transdermal testosterone therapy among surgically induced menopausal women with HSDD on a stable dose of oral estrogen with or without progestin (N=549) (Shifren et al., 2006). Women were randomized to receive testosterone 300 mcg/day or placebo patches twice weekly for 24 weeks. The primary efficacy measure was change from baseline in frequency of total satisfying sexual activities over a four-week period. The results demonstrated that there was a change in the number of total satisfying sexual episodes for the participants on testosterone compared with placebo. The results also demonstrated that testosterone also produced statistically significant improvements compared with placebo in all secondary efficacy measures, including sexual desire and personal distress. Furthermore, the patch was well tolerated (Shifren et al., 2006).

INTIMATE NM2. This study used the same instruments for assessments of FSD as in the INTIMATE NM1 study and the participants had surgically induced menopause. Five hundred and thirty-two surgically induced postmenopausal women aged 31 to 56 years with HSDD were randomly assigned to either a 300-mcg/day-testosterone patch or placebo with either oral or transdermal estrogen. Testosterone recipients reported an increase of 1.56 satisfying sexual episodes per four weeks versus 0.73 episodes per four weeks with placebo, an increase from 51% versus 23% from baseline for each group. Overall, sexual desire increased 49% from baseline in the testosterone group (Krapf & Simon, 2009).

APHRODITE. This phase three trial studied testosterone's safety and efficacy in women not taking concurrent estrogen therapy. The women from 65 centers in the US,

Canada, Sweden, and the United Kingdom participated between 2004 and 2006. In this study Davis et al. (2008) conducted a double-blinded placebo controlled trial of 814 women with HSDD who were not currently taking estrogen. The women were randomly assigned to a 150 mcg/day-testosterone patch, a 300 mcg/day-testosterone patch, or placebo patch. The primary endpoint of frequency of satisfying sexual episode in addition to assessment of FSD using the SAL, PFSF, and PD scale were measured after a 24-week trial period (Davis et al., 2008). Safety was assessed throughout week 52 and an optional extension phase was continued for an additional year.

Consistent with the results in the INTIMATE studies, there was an increase in the number of sexually satisfying episodes in the women receiving 300-mcg/day testosterone patches, but not in the 150-mcg group (Davis et al., 2008). The 300-mcg group reported 2.1 satisfying sexual episodes per four weeks, versus 0.7 episodes in the placebo group, which equates to 78% sexually satisfying experienced on the higher testosterone group compared to 65% for placebo (Davis et al., 2008). The 300-mcg group also reported higher scores for sexual desire and decreased scores for personal distress (Krapf & Simon, 2009). The rate of androgenic adverse effects, primarily unwanted hair growth, was higher in the group receiving 300 mcg/day of testosterone than in the placebo group (30% vs. 23.1%). Breast cancer was diagnosed in four women who received testosterone, as compared to none who received placebo. One of the four received the diagnosis in the first four months of the study period, and one in retrospect had symptoms before undergoing randomization. The primary reasons for withdrawal were application site reactions. Clitoral enlargement happened in four women receiving testosterone; however, none of these women withdrew from the study and subsequent examination

revealed resolution (Davis et al., 2008). The groups did not differ significantly in respect to serum lipid profiles.

ADORE. The ADORE study sought to evaluate the efficacy and safety of a transdermal testosterone patch of 300 mgs/day in naturally menopausal women with HSDD. A total of 272 naturally menopausal women who were predominantly not using hormone therapy were randomized in this six-month, placebo-controlled, double-blind, multicenter study to receive twice weekly of either transdermal testosterone or an identical placebo. Efficacy endpoints measured were the four-week frequency of satisfying sexual episodes (SSE) using the Sexual Activity Log, the sexual desire domain of the Profile of Female Sexual Function and distress by the Personal Distress Scale. Safety was assessed by monitoring adverse events, laboratory parameters, and hormone levels (Panay et al., 2010).

The transdermal testosterone group demonstrated significant improvements in SSE as well as in sexual desire and reduced personal distress versus placebo at six months. Similar numbers of women treated with placebo and transdermal testosterone withdrew from the study due to adverse events including application site reactions. Serum free and total testosterone levels increased from baseline in the transdermal testosterone group within the physiological range. The conclusion of the study was that transdermal testosterone was effective in treating HSDD and improving sexual dysfunction in naturally menopausal women with and without concurrent hormone therapy (Panay et al., 2010).

Phase two trials. Shifren and colleagues (2000) conducted the first randomized, double-blinded placebo controlled study of a transdermal testosterone patch. Seventy-

five surgically induced menopausal women aged 31 to 56 years with self-reported impaired sexual dysfunction taking estrogen therapy were randomly assigned to either a 150 mcg/day testosterone patch, a 300 mcg/day testosterone patch, or placebo. Women receiving 300 mcg/day of testosterone reported significantly higher scores for frequency of sexual activity, sexual fantasies, masturbation, and orgasm than those in the lower testosterone group (Shifren et al., 2000).

Another phase two trial followed in 2005, which included a larger patient population, a longer treatment period, and a higher dosage group. Braunstein et al. (2005) randomized 318 surgically induced menopausal women with HSDD who were already receiving oral estrogen therapy to a 24-week period of varying doses of the testosterone patch (150 mcg/day, 300 mcg/day, or 450 mcg/day), or a placebo. This study used three validated efficacy instruments to assess FSD: The Profile of Female Sexual Function (PFSF), the Profile of Sexual Activity (SAL), and the Personal Distress Scale (PDS). Interestingly, significant increases in sexual desire and frequency of satisfying sexual activity were found only in the 300-mcg group compared with placebo (sexual desire increased 67% from the baseline verses an increase of 48% with placebo and sexually satisfying experiences increased 0.58 each week). No treatment effect was seen in the 150 mcg/day or in the 450 mcg/day, which raised the suspicion of a testosterone dose curve. Of note, frequency of adverse events was similar among all groups with no severe events reported (Braunstein et al., 2005).

Small community based trials of testosterone's efficacy on surgically induced menopausal participants. In 2007 El-Hage et al. (2007) conducted a double-blind cross over study that included hysterectomized postmenopausal women who were already

taking transdermal estrogen. The 36 menopausal healthy women who were recruited had undergone a hysterectomy, were not depressed, were in a stable relationship, and filled the diagnostic criteria for low sexual desire, as measured by the Brief Index of Sexual Function for Women (BISF-W) (El-Hage, Eden, & Manga, 2007). The researchers found that 10 mgs of topical cream significantly improved sexual desire, frequency of sex, receptivity, and initiation of sex as measured by the BISF-W (El-Hage et al., 2007; Krapf & Simon, 2009).

In another study, a representative sample of 132 surgically postmenopausal women with HSDD was enrolled in two randomized, placebo-controlled trials (N=1094) that assessed the efficacy and safety of transdermal testosterone treatment (300 mcg/day) for 6 months. At the end of the study, prior to un-blinding, a sample of women (12%) was interviewed concerning their experiences with the treatment. The conclusions were that surgically menopausal women with HSDD received clinically meaningful benefits, including improvements in satisfying sexual activity, sexual desire, and personal distress (Kingsberg et al., 2007).

Small community based trials of premenopausal women with low libido.

Premenopausal women with low libido participated in a randomized, placebo controlled, crossover efficacy study of testosterone cream (10 mg/day) with two double-blind, 12-week, treatment periods separated by a single blind, four-week washout period. Thirty-four women completed the study and 31 provided complete data. Testosterone therapy resulted in a statistically significant improvement in the composite scores of Psychological General Wellbeing Index and the Sabbatsberg Sexual Self-Rating Scale compared with placebo. A mean decrease in the Beck Depression Inventory score

approached significance. Mean total testosterone levels during treatment were at the high end of normal range and estradiol was unchanged. Conclusions were that testosterone therapy improved wellbeing, mood, and sexual dysfunction in premenopausal women (Goldstat et al., 2003).

Cochrane reviews. Two Cochrane reviews have recently examined the benefits and risks of testosterone therapy plus estrogen-progestin (EPT) versus EPT alone for perimenopausal and postmenopausal women by including 35 studies with 4,768 participants. The majority of the trials included both naturally and surgically postmenopausal women. Testosterone regimens included oral tablets, intramuscular injections, subcutaneous implants, and transdermal patches and gels. The median study duration was six months (range 1.5–24 months). The pooled estimate from the clinical trials suggested that the addition of testosterone to hormone therapy regimens improved sexual function scores and number of total satisfying sexual episodes in postmenopausal women. Beneficial effects were seen for the composite sexual function score and domains of sexual activity, coital frequency, responsiveness, and desire (Nappi et al., 2010).

Testosterone side effect and safety profile. The findings and conclusions from many smaller studies are similar to the results found in a MEDLINE literature review, cross-reference of published data, and review of the FDA, all of which critically examined the safety of testosterone therapy given to menopausal women (Braunstein, 2007). The broad conclusions are that except for hirsutism and acne with or without estrogen, the administration of transdermal testosterone in physiologic doses is safe. However, long-term safety of testosterone as a hormone replacement therapy has not

been well established because the majority of prospective studies ranged from one to two years (Braunstein, 2007; Davis & Braunstein, 2012; Shufelt & Braunstein, 2009). Thus, prospectively collected long-term studies are needed to provide a greater degree of assurance (Davis & Braunstein, 2012; Shufelt & Braunstein, 2009).

Short-term safety has been demonstrated with many randomized, placebo-controlled studies as well as the documented side effects (Davis & Braunstein, 2012). As already mentioned, the most common side effects of testosterone therapy include mild and reversible acne and hirsutism, which has been observed in the use of testosterone with and without estrogen. These side effects are thought to be dose dependent (Braunstein, 2007; Shufelt & Braunstein, 2009). Virilization such as deepening of the voice and clitoromegaly are rare with low dose therapy and has not been at all observed in menopausal women treated with physiologic doses for HSDD (Braunstein, 2007; Davis & Braunstein, 2012). Changes to the lipid profile such as decreasing high-density lipoprotein (HDL) was noted with oral, but not transdermal testosterone, which bypasses hepatic metabolism (Davis & Braunstein, 2012; Shufelt & Braunstein, 2009).

The major safety concerns surrounding testosterone therapy in women are related to potential adverse effects on the cardiovascular system and stimulation of the endometrium and breast tissue leading to carcinoma. Liver toxicity and behavioral effects have also been called into question (Braunstein, 2007; Davis & Braunstein, 2012). Short-term studies of up to two years have shown that for serum plasma testosterone levels at the upper portion or slightly above the reference range for reproductive aged women, testosterone does not increase the risk of hepatotoxicity, endometrial hyperplasia, or behavioral hostility. No adverse cardiovascular effects including changes

in blood pressure, blood viscosity, arterial vascular reactivity, hypercoagulable states, and polycythemia have been shown (Shufelt & Braunstein, 2009). The side effects and safety profile that have been most scrutinized are related to breast and cardiovascular health; however, while testosterone does not appear to adversely impact either of these conditions, it is thought that it may provide a protective effect (R. L. Glaser & C. Dimitrakakis, 2013).

Breast cancer. Concerns have been raised that either directly or indirectly androgens stimulate the development or growth of breast cancer despite of the fact that androgens have been used to treat breast cancer (Braunstein, 2007; Hofling et al., 2007). Data is mixed with outcomes of breast cancer risk with some experimental studies suggesting a decrease in estrogen-induced breast epithelial proliferation with low dose testosterone. There are no randomized trials that show a risk between breast cancer and testosterone therapy, although four participants in the APHRODITE phase three trial developed breast cancer in the testosterone group (Davis et al., 2008; Feldhaus-Dahir, 2009a).

Feldhaus-Dahir (2009b) discussed the method and results of a retrospective observational study regarding breast cancer and hormone replacement therapy in 2004, which showed that among 508 postmenopausal women reviewed over a mean of 5.8 years, the incidence of breast cancer was not different among those who used estrogen alone, those who combined estrogen with testosterone, or those who used no hormones at all. It is now understood that postmenopausal exogenous use of estrogen is associated with an increase in breast cancer. Additionally, models of super-physiologic testosterone levels, such as in polycystic ovarian syndrome (PCOS) or in female to male transgender

individuals have not shown an increased risk of breast cancer (Davis & Braunstein, 2012).

The first six-month prospective, randomized, double-blind, placebo-controlled prospective study that measured the effects of testosterone on breast cell proliferation was performed on 99 postmenopausal women (Hofling et al., 2007; Krapf & Simon, 2009). Hofling et al. (2007) gave the participants estrogen and progestin and then randomized to transdermal testosterone or a placebo patch. Fine needle aspiration biopsies were taken at baseline and at six months to evaluate the epithelial and stromal cell proliferation. There were no significant differences for the women who were randomized to testosterone, while there was more than a five-fold increase in breast cell proliferation in women on an estrogen-progestin placebo patch (Davis & Braunstein, 2012; Hofling et al., 2007).

The effects of exogenous testosterone on breast cancer risk remain unclear. Of eight observational studies in populations receiving testosterone alone or in combination with estrogen or estrogen/progestin, only two reported a significant increase in breast cancer. Among these, a retrospective cohort study suggested an increased risk of breast cancer in women taking exogenous testosterone, primarily methyltestosterone, but other studies showed inconsistent associations. Of note, these studies were known to have methodological problems, including but not limited to a small sample size and a lack of matches for other breast cancer risk factors (Davis & Braunstein, 2012).

Evidence from other studies has suggested that androgens are breast protective. To investigate the incidence of breast cancer in women who were treated with subcutaneous testosterone therapy in the absence of systemic estrogen therapy, a five-year interim analysis of a 10-year, prospective, observational study investigated the

incidence of breast cancer in women who presented with symptoms of hormone deficiency treated with subcutaneous testosterone implants or testosterone combined with the aromatase inhibitor (AI) anastrozole implants. Breast cancer incidence was compared with that of historical controls reported in the literature, age specific Surveillance Epidemiology and End Results (SEER) incidence rates, and a representative, similar age group of patients used as a control group. The effect of adherence to testosterone therapy was also evaluated (R. L. Glaser & C. Dimitrakakis, 2013).

Since March 2008, 1,268 pre-and-post-menopausal women have been enrolled in the study and eligible for analysis. As of March 2013, there have been eight cases of invasive breast cancer diagnosed in 5,642 person-years of follow up for an incidence of 142 cases per 100,000 person-years, which is substantially less than the age-specific SEER incidence rates (293/100,000), placebo arm of Women's Health Initiative Study (300/100,000), never users of hormone therapy from the Million Women Study (325/100000), and the control group (390/100,000). Unlike adherence to estrogen therapy, it was discovered that adherence to testosterone therapy further decreased the incidence of breast cancer (73/100,000) (R. L. Glaser & C. Dimitrakakis, 2013).

Furthermore, testosterone and/or testosterone and anastrozole reduced the incidence of breast cancer in premenopausal and postmenopausal women. The evidence supported that breast cancer is preventable by maintaining a testosterone to estrogen ratio in favor of testosterone and, in particular, the use of continuous testosterone or when indicated testosterone and anastrozole. The final summary and conclusion were that testosterone hormone therapy has been recommended for further investigation for the prevention and treatment of breast cancer (R. L. Glaser & C. Dimitrakakis, 2013).

Lending to the above-mentioned studies is the knowledge that women with breast cancer have better cancer-related outcomes with the use of AIs, but the physiological suppression of estradiol can negatively affect sexual functioning because of unpleasant urogenital and vaginal symptoms (Dahir & Travers-Gustafson, 2014). Therefore, a pilot study was conducted to research the effects of vaginal testosterone therapy on sexual quality of life in women with breast cancer taking AI therapy. Thirteen postmenopausal women with breast cancer on AI therapy and experiencing symptoms of sexual dysfunction were recruited from an oncology practice. The women were prescribed a 300- μ g testosterone vaginal cream daily for four weeks. The Female Sexual Function Index (FSFI) survey, measuring female sexual health quality of life, was administered during the first study visit and at the final study visit after completing testosterone therapy. Twelve patients completed four weeks of daily vaginal testosterone therapy. When compared with baseline FSFI scores, there was a statistically significant improvement for individual domain scores of desire, arousal, lubrication, orgasm, satisfaction, and pain. Total domain scores reflecting sexual health quality of life also improved when compared with baseline. The conclusions were that the use of a compounded testosterone vaginal cream applied daily for four weeks improves reported sexual health quality of life in women with breast cancer taking AIs (Dahir & Travers-Gustafson, 2014).

Cardiovascular disease. There have been no associations between endogenous levels of testosterone in women and coronary artery disease (CAD) and in some cases a protective effect had been shown (Braunstein, 2007; Davis & Braunstein, 2012; Shufelt & Braunstein, 2009). Prospective studies do not support a causal role of high

endogenous androgen levels in cardiovascular events or deaths in older women (Davis & Braunstein, 2012). In a study of 693 women with and without established CAD, age adjusted levels of androgens showed no statistical difference. Androgen levels were not predictive of cardiovascular death in this cohort that was followed for 19 years (Braunstein, 2007; Shufelt & Braunstein, 2009). In another population-based study with a median follow-up of 12.3 years, it was noted that the optimal range for testosterone-promoted cardiovascular health with an increased risk for cardiovascular events at the upper and lower levels of bioavailable testosterone (Davis & Braunstein, 2012).

Testosterone treatment in women at the doses used for treating HSDD has been found to not adversely affect the cardiovascular safety profile (Davis & Braunstein, 2012). Lipid alterations noted with exogenous testosterone appear to be dependent on the route of administration. Because of the first pass effect, changes in the lipid profile and particularly a reduction in the HDL cholesterol are observed with oral testosterone given concomitantly with estrogens, whereas transdermal testosterone administered with estrogen has been shown to be lipid-level neutral. In a two-year study on clotting factors, no differences in levels of fibrinogen, thrombotic, or fibrinolytic proteins were observed in women who were receiving testosterone subcutaneous implants (Davis & Braunstein, 2012). Polycythemia has not been reported in women receiving physiologic doses of testosterone and the large doses of testosterone used to treat female-to-male transgender subjects increase hemoglobin only to the level found in normal healthy men (Davis & Braunstein, 2012).

While women with PCOS have hyperandrogenemia as well as an increased risk of CAD, the mechanism is believed to be secondary to hyperinsulinemia related to visceral

obesity, insulin resistance, and dyslipidemia. Adding to this, studies show that physiologic doses of testosterone either oral or transdermal does not lead to insulin resistance or a change in fasting glucose. Additionally, the authors reported no cardiovascular mortality over 2,418 patient-years of treatment in 293 female-to-male transsexuals who received male testosterone replacement doses from two months to 41 years. There was only one case of a myocardial infarction and angina and 12 patients had increased blood pressure (Davis & Braunstein, 2012).

Endometrial effects. It is thought that any stimulatory effects of testosterone on the endometrium would occur via local aromatization to estrogen, but aromatase activity has not been detected in the endometrial environment. Thus, testosterone should not have adverse uterine effects. In an examination of endometrial biopsies from postmenopausal women before and after three months of treatment with oral testosterone alone, estradiol alone, or both provided direct evidence that testosterone did not have adverse uterine effects, whereas the women taking estrogen alone showed proliferative changes that increased by 50%. Combined treatment resulted in a non-significant increase to 28%, which suggested that testosterone might counteract estrogen-induced proliferation. These findings are similar to the results from the APHRODITE study, where treatment with testosterone did not result in any adverse endometrial assessed over 12 months by trans-vaginal ultrasound and endometrial biopsy (Davis & Braunstein, 2012). Additionally, there were no cases of endometrial hyperplasia.

Other safety concerns. No trials to date of transdermal testosterone have reported liver toxicity nor has there been any hepatic dysfunction noted in trials of oral estrogen plus testosterone (Davis & Braunstein, 2012). Additionally, there have been studies that

demonstrate that testosterone therapy decreased aggression, hostility, and anxiety in women and may even improve depression severity (R. Glaser & C. Dimitrakakis, 2013; Miller et al., 2009). However, high doses of endogenous testosterone in female students were correlated with financial risk taking behavior and reduced interpersonal trust, particularly in highly trusting women (Davis & Braunstein, 2012).

A safety study of LibiGel (testosterone gel). Evaluation of the safety of hormonal preparation for the treatment of FSD is important to assess the benefit-to-risk profile of these drugs and has been strongly encouraged by the FDA. The LibiGel Safety Study (BLISS) is the first large, long-term safety study of oophorectomized postmenopausal women aged 30-65 with HSDD receiving a dose of testosterone equal to ovarian production rate in younger women with normal menstrual cycles. The study was enriched by including participants with an elevated CV risk (White et al., 2012).

LibiGel, a low-dose testosterone gel, is under development for the treatment of HSDD (White et al., 2012). To evaluate the long-term effects of LibiGel on risk for CV events, breast cancer, and general safety, a long-term randomized placebo controlled parallel group clinical study using a novel adaptive design to optimize sample size and power is currently being conducted with applications of 0.22 grams/day. The primary endpoint of the BLISS study is a composite of CV events including death, nonfatal myocardial infarction, nonfatal stroke, coronary vascularization, hospitalized unstable angina, and venous thrombotic events. Breast cancer is a co-primary endpoint.

The active treatment phase of the study is longer than former studies and consists of 60 months of drug exposure. The study had enrolled more than 2500 postmenopausal women with more than 2,200 women-years of exposure accrued. Following four

unblinded safety reviews by an independent data monitoring committee, the composite adjudicated cardiovascular event was 0.65% and breast cancer rate was 0.32%. The conclusions thus far in this ongoing study conclude that low event rates in women at the higher end of the cardiovascular risk continuum for the intended treatment population support the lack of cardiovascular and breast cancer risk of testosterone (Davis & Braunstein, 2012).

Intra and Vulvovaginal testosterone. There is thought to be a greater incidence of vaginal atrophy in women on AIs for breast cancer. The need for a safe and effective nonestrogen therapy for vaginal atrophy led to a study where 21 postmenopausal breast cancer patients on AI therapy with vaginal atrophy were treated with testosterone cream applied to the vaginal epithelium daily for 28 days. A 4-week course of vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to aromatase therapy without increasing estradiol levels (Witherby et al., 2011).

In another study, 75 postmenopausal women symptomatic for urogenital atrophy and sexual dysfunction were randomly divided into two study groups and one control group (Raghunandan, Agrawal, Dubey, Choudhury, & Jain, 2010). The women in study group one received local estrogen cream, study group two received local estrogen and testosterone cream, and the control group received non-hormonal lubricant KY gel for 12 weeks. The Urogenital and Sexuality score, the Vaginal Health Index, and the Vaginal Maturation Index (VMI) were calculated at the beginning of therapy and 12 weeks later and served as the main outcome measures.

After 12 weeks of therapy, there was a significant improvement in all the study parameters, which correlated well with the improvement in symptoms of urogenital

atrophy and sexual dysfunction in both study groups as compared with the control group. Improvement in sexuality score was greatest with combined estrogen-androgen therapy. There were no adverse effects noted and the therapies were well accepted without any compliance issue. Local estrogen either alone or with an androgen such as testosterone were considered to be highly effective in relieving symptoms of urogenital atrophy and in improving sexual function in symptomatic postmenopausal women (Raghunandan et al., 2010).

In another study based on a literature review, it was concluded that oral, transdermal, or vaginal estrogen preparations are the most effective treatment options for vulvovaginal atrophy-related sexual dysfunction, though vaginal dehydroepiandrosterone and vaginal testosterone are emerging as promising new therapies; however, it has been concluded that further studies are warranted to confirm efficacy and safety (Tan, Bradshaw, & Carr, 2012).

Testosterone, the controversy. It has been suggested that to prepare the market for a testosterone patch, HSDD was established by the medical and pharmaceutical industry in 2004 to sell product by medicalizing female sexuality. Some researchers feel that the efficacy and safety concerns over administration of testosterone for this disorder have been trivialized and the potentially modest benefits have been overblown. For example, the results of a 24-week randomized controlled trials of testosterone trials showed the testosterone patch increased the amount of satisfying sexual activity for women by around two episodes a month compared with the baseline which amounted to one extra episode compared with the placebo response. These trials made some researchers question if the women enrolled were even dysfunctional being that the

amount of sexual episodes described were considered to be average in long term relationships (Moynihan, 2005).

It has also been noted in the literature that many of the experts involved in testing the patch and in advocating for its approval had financial conflicts of interest. An example given by Moynihan (2005) was that at least two of the senior academic investigators who tested the patch also ran private for-profit research companies that contracted with Proctor and Gamble to help carry out the clinical trials. Of note, it was Proctor and Gamble who attempted to market a testosterone patch to women who became menopausal after ovarian surgery and reportedly suffered from HSDD. Further, Harvard University Professor, Jan Shifren, a strong advocate of the testosterone patch had presented at medical events funded by unrestricted educational grants from Proctor and Gamble, and that she was a paid member of the company's advisory board (Moynihan, 2005). Shifren rejected the notion that the testosterone patch only showed modest increases in sexual activity and proposed that the way a woman feels about their desire problems and related distress are the key issues.

Critics of testosterone for HSDD noted that the decrease in distress over placebo was only six or seven points on a 100 scale which raised serious questions about the meaningfulness of the purported benefits. Though the FDA advisors voted to accept the patch benefits as clinically meaningful, they unanimously rejected the testosterone patch company's data as inadequate to assess long term safety, and unanimously recommended the agency not to improve the drug (Moynihan, 2005). It was concluded that:

The pharmaceutical industry's strong commercial interest in this area may

ultimately bring benefits to women, through the development of safe and effective medicines, and through an increased understanding of female sexuality. Yet, if those desirable benefits are to be achieved, we might have to start relying a little less on marketing and promotional campaigns about new diseases, dressed up in science and education. (Moynihan, 2005, p. 194).

Conclusion. Early studies established that testosterone therapy improved sexual desire and activity in both naturally and surgically induced menopausal women. Adverse side effects were primarily noted to be dose-dependent and androgenic in nature. Research was then conducted to explore a more efficacious administration route. Transdermal delivery of testosterone was discovered to have advantages in that this delivery route avoided first pass hepatic metabolism and delivered a more consistent physiologic dose. Many studies have shown that physiologic doses of approximately 300 mcg/day are both efficacious at treating HSDD and have a low side effect profile (R. Glaser & C. Dimitrakakis, 2013; Nappi, 2015b). Studies have shown that transdermal testosterone is considered safe for short-term application and may even have a cardio-protective effect and reduce the likelihood of estrogen-dependent breast cancer.

Nevertheless, there remains a controversy surrounding the application of testosterone for HSDD, primarily based over concerns that experts involved in testing the patch and advocating for its' approval had financial conflicts of interest. Some researchers have purported that the safety and efficacy have been trivialized, while its benefits have been overblown; however, the literature backing these claims pales in comparison to the large body of work that demonstrate the effectiveness and safety of physiologic doses of testosterone for hypoactive sexual desire and/or low libido.

Further, the timeline of events which came to be called the “Campaign for a New View of Women’s Sexual Problems” that in part challenged the pharmaceutical industry’s “aggressive interest in sex” and FSD “disease mongering” have been overshadowed by the Endocrine Society’s stance on the matter, after a panel of experts critically reviewed the research and suggested its use in targeted situations for HSDD (Tiefer, 2006).

Primary Care and HSDD

Abdolrasulina et al. (2010) asserted that 40% of women report female sexual problems, particularly sexual desire disorders and that there are numerous practical, professional, and personal barriers to the evaluation, diagnosis, and management by treating healthcare providers. Additionally, sexual complaints usually arise in the context of other physical, psychological, and relationship issues (Parish, 2009).

Though sexual dysfunction is common in women and is associated with distress and burden as noted in key findings from large population-based studies, it remains underdiagnosed and undertreated (Nappi et al., 2010). In part, this may be due to a patient’s reluctance to discuss it with their provider even when specifically asked about it. It is estimated that only 18% of women with sexual concerns will spontaneously volunteer information about sexual dysfunction with their healthcare provider (Wright & O'Connor, 2015).

It is the duty of healthcare providers to inquire about their female patient’s sexuality because sexuality may impact the quality of the patient’s life or be a quality of life indicator (Zakhari, 2009). Engaging in conversation about sexuality with the menopausal patient may be difficult due to the many barriers, prohibitive factors, and

misconceptions healthcare providers have regarding menopausal sexuality, including the idea that sexual problems are a normal part of aging and long relationships, and therefore, do not deserve specific treatments (Abdolrasulnia et al., 2010; Nappi et al., 2010).

Discussions with patients about menopause-related HSDD may be inhibited by medical literature that questions whether HSDD is a medical condition warranting intervention with pharmacological treatment (Meixel et al., 2015; Tiefer, 2006).

Additionally, the multitude of determinants of sexual desire across the life cycle, and the difficulties in establishing the level of discrepancy between expected and current desire in a specific relational context bring about the idea that HSDD is a condition difficult to treat. Moreover, the healthcare providers personal experiences and cultural norms may modulate the inquiry into female sexuality and FSD, especially in menopause (Nappi et al., 2010).

Studies related to practice patterns, perceptions, and barriers to the diagnosis and management of FSD. To identify practice patterns, perceptions, and barriers to the diagnosis and management of female sexual problems among US practicing primary care physicians and obstetricians/gynecologists, a random sample was sent a case vignette survey by e-mail and fax to study the frequency and variability in diagnostic tests ordered and treatment recommendations provided for the patient with HSDD (Abdolrasulnia et al., 2010). A total of 505 responses were analyzed (8.8% response rate).

Of the respondents, 21% of OB/GYNs and 38% of PCPs stated they were not at all confident in treating HSDD. The majority of physician respondents ordered a thyroid panel to assess diminished desire and recommended counseling and stress reduction

therapies to the female patient with sexual complaints. Results of the study identified time constraints, the perceived lack of effective therapies, perceptions regarding patient-physician gender discordance, years in practice, number of patient seen per week, and perceptions regarding continuing medical education and practice experience as significant an independent predictor of confidence in treating HSDD patients. The conclusions were that discussion of sexual health is difficult and that there are predictors of confidence in treating patients with decreased desire. Both PCPs and OB/GYNs rated the perceived lack of effective therapies as a significant challenge to initiating dialogue with patients about sexual problems. Time constraints were also considered to be a moderate barrier to both groups. Both groups perceived gender differences as a significant barrier to initiating dialogue as well (Abdolrasulnia et al., 2010).

In another large population-based sample of 1,154 practicing OB/GYNs (53% male; mean age 48 years) was surveyed regarding their practices of communication with patients about sexuality and to examine the individual and practice-level correlates of such communication. The survey response rate was 65.6%. Sixty-three percent of OB/GYNS reported routinely assessing patient's sexual activities and 40% routinely asked about sexual problems. Fewer asked about sexual satisfaction (only 28.5 %) or pleasure with sexual activity (13%). A quarter of OB/GYNs practicing reported that they had expressed disapproval of patient's sexual practices. The conclusions of the study were that the majority of US OB/GYNs reported routinely asking patients about their sexual activities but most other areas of patient's sexuality are not routinely discussed (Sobecki et al., 2012).

In one small pilot study, all residents and faculty in an academic primary care clinic were invited to participate in a web-based survey regarding HSDD that included a 10-item questionnaire regarding HSDD. In total, 53 of the 155 physicians responded (34% response rate). Of the respondents, 90% reported little confidence in making the diagnosis of HSDD, 90% of the physicians had not screened a patient for HSDD, and 98% of the physicians had not prescribed medication for patients for HSDD. The results indicated that there was an opportunity to improve patient care and life satisfaction by offering physicians training on diagnosis and management of HSDD (Harsh et al., 2008).

An internet-based survey was constructed to evaluate third and fourth year residents in American Council for Graduate Medical Education-approved OB/GYN programs. Residents were asked about familiarity, knowledge, and confidence in treating various aspects of female sexual function and dysfunction. Two hundred and thirty-four residents responded. Only 19.6% reported often or always screening women for sexual function problems; most had very little knowledge in administering or interpreting questionnaires. Many felt confident about obtaining a complete sexual history; however, only a minority of 18.4% had managed women with low desire. The conclusions were that despite CREOG requirements for OB/GYN training in female sexuality, most residents felt ill equipped to address these problems (Pancholy et al., 2011).

Biological and sociocultural differences between men and women may play an important role in medical treatment (Loikas et al., 2015). In one study, PCPs stated they had little knowledge of sex and gender differences in drug treatment, but gave multiple examples of how the patient's sex affects the choice of treatment (Loikas et al., 2015). This indirectly correlates with the aforementioned study of OB/GYN practices where

female OB/GYNs were significantly more likely than males to routinely ask patients about sexual activity.

Primary care and testosterone for HSDD. In one study, interviews and an opinion poll of gynecologists and family medicine physicians were conducted to identify the current prescribing pattern of off-label testosterone use in treating HSDD. The Intercontinental Marketing Services (IMS) prescription review showed that two million testosterone prescriptions were written for women in 2006 and 2007, many of which were compounded testosterone. Based on a summary of the physicians' survey on average patients of all ages, but particularly menopausal women, have at least moderate awareness of HSDD. More than 80% of physicians believe that there is a need or great need for a FDA approved HSDD treatment and 90% of physicians surveyed would prescribe an approved HSDD product over currently prescribed therapy (Snabes & Simes, 2009).

Summary

Researchers have concluded that the healthcare provider needs to be aware of all the potential influences leading to HSDD, including their own biases and perceptions including the underestimation of the prevalence of sexual dysfunction or its impact on quality of life (Frank et al., 2008). Discomfort with the topic, difficulty with the diagnosis, lack of provider confidence, inadequate training, limited treatment options, and insufficient clinical time with the patient to discuss in depth sexual histories all contribute to inadequate management of female sexual problems, namely menopause related HSDD (Frank et al., 2008; Wright & O'Connor, 2015).

It is suggested that treatment for menopause-related HSDD should encompass a holistic multidisciplinary approach including counseling, psychosexual therapy, and appropriate evidenced-based pharmacotherapy. The approach to management should address any factors that might be amenable to intervention, whether or not they constitute the primary cause of the complaint of loss of libido (Parish, 2009). With improved access to medical care and nutrition, the average life expectancy for women is increasing along with an interest in maintaining sexual function.

Though testosterone has been utilized for decades for various disorders and conditions and has demonstrated its safety and efficacy, it is still an underutilized treatment for low libido and diminished sexual desire in the naturally occurring menopausal female. One researcher summarized his life-long work with testosterone by stating the following:

Today, there is a dominant narrative that the benefits of TTh [testosterone therapy] are unproven, the risks are substantial, and TTh is abused and overused because of physicians yielding to unwarranted demand by misguided patients who are unwilling to accept normal aging. Although there is no evidence to support this position, and considerable evidence to the contrary, this narrative has trumped the facts within the public media. The impact of this vilification of TTh has been substantial, discouraging symptomatic patients from accepting a potentially beneficial treatment, and generating suspicion of physicians offering TTh by their colleagues, for questionable medical practices. This is unfair to patients and physicians alike (Morgentaler, 2016).

HSDD in naturally occurring menopause is considered by some to be medicalization of a normal state where providers of healthcare are persuaded by the pharmaceutical industry to meet an unmet need with pharmaceutical interventions, such as testosterone, in order to sell a product. The average woman making the transition into menopause can expect to live for at least 25 years and with the increased expectations for a longer and healthier life, women are more interested in maintaining sexual function (Thornton et al., 2015). If sexuality is a quality of life indicator and primary care providers and providers of gynecologic healthcare are encouraged to treat patients holistically, then help with maintaining a patient's sexuality (if it is important to that particular patient) falls within their scope of practice.

Gaps in the Medical Literature

To gain a deeper understanding of why testosterone remains underutilized by the medical community in the primary care setting for low libido and diminished sexual desire in menopause despite its proven efficacy and safety, gaps in the medical literature were critically analyzed.

First, it is unclear in the medical literature if primary care providers and providers of gynecological healthcare consider low libido and diminished sexual desire in the naturally occurring menopausal female to be a medical condition or disorder, a natural part of aging, or both and whether or not their opinion on the matter would impact evaluation, diagnosis, and/or the choice of treatment for this problem.

Secondly, while there are ample studies in the literature that demonstrate low libido and diminished sexual desire are the most common female sexual complaints and that these problems cause considerable distress and interpersonal difficulties, especially

in menopause, there remains a paucity in the literature regarding provider's perceptions, knowledge, and experiences regarding pharmaceutical treatment for these complaints. Furthermore, there is paucity of literature about provider's knowledge of and experience with testosterone, specifically for HSDD, in naturally occurring menopausal women. Additionally, there has been very little discussion in literature that questions whether estrogen unopposed by testosterone may be a cause or contributing factor in the increased risk of breast and endometrial cancer.

Lastly, while the literature speaks to closing the gender gap in sexual medicine, it does not specifically challenge the medical establishments as to why testosterone cannot be prescribed or suggested for menopausal women who are not in any particular distress and/or not having interpersonal difficulties seeking to maintain their sexual function and sexual satisfaction and who are "otherwise healthy."

Chapter 3: Methods

Sample, Subjects, and Setting

As this research involves human subjects, it underwent a review and approval from the University of Vermont Institutional Review Board (IRB) prior to initiation of the study. The IRB determined the study to be exempt (See Appendix A). Respondents in this study were a convenience sample of primary care providers (PCPs) and gynecologic health care providers. The inclusion criteria included those PCPs who are currently practicing or have practiced in the last two years in the primary care setting for the care of menopausal women primarily in the professional role of physician, nurse practitioner or physician assistant. Recruitment for this study was accomplished through listservs of the following Vermont-based professional organizations: the Vermont Nurse

Practitioners Association (VNPA), the Vermont Academy of Family Physicians (VTAFP), and the Physician Assistant Academy of Vermont (PAAV).

The inclusion criterion was specified in the electronic mailings along with notification that participation in the survey will be considered consent. Participation in the survey was voluntary. The respondents remained anonymous throughout the survey process and thereafter.

Design

The study design was a descriptive cross-sectional online LimeSurvey. The LimeSurvey was sent out electronically to listserv e-mails of potentially eligible respondents on a secure server through the University of Vermont.

At the beginning of the survey, the respondents were informed that participation in the study was both voluntary and anonymous. Anonymity remained throughout the survey process and thereafter. Respondents had to meet inclusion criteria, which were established by answering a single question at the beginning of the survey: Are you a primary care provider or provider, a gynecologic health care provider, or a specialty provider who is currently practicing or who has practiced within the last two years with a patient population that includes naturally occurring menopausal females? If the respondents met the inclusion criteria, they were asked to proceed with the survey questionnaire. Respondents were asked to answer the questions as accurately as possible.

After the initial invitation to participant in the online LimeSurvey was submitted on October 7, 2016 it was available to the respondents for completion for three weeks afterwards by the end date of October 28, 2016.

Instrument and Data Collection

The instrument of study was a cross-sectional online survey of PCPs and providers of gynecologic healthcare in the state of Vermont. Data collection was through LimeSurvey, an online server-based software that collected responses, generated statistics, and exported the resulting data to other applications. Content validity of the online survey was established through a comprehensive literature review as well as a review by a panel of experts in the field of women's health. Reliability was not established.

Data Analysis

Following the conclusion of the descriptive cross-sectional online survey, the data was exported to a Microsoft Excel Spreadsheet through the LimeSurvey software. The data was analyzed using descriptive statistics and was critically examined.

Chapter 4: Results

Section One: Respondent Inclusion Criteria.

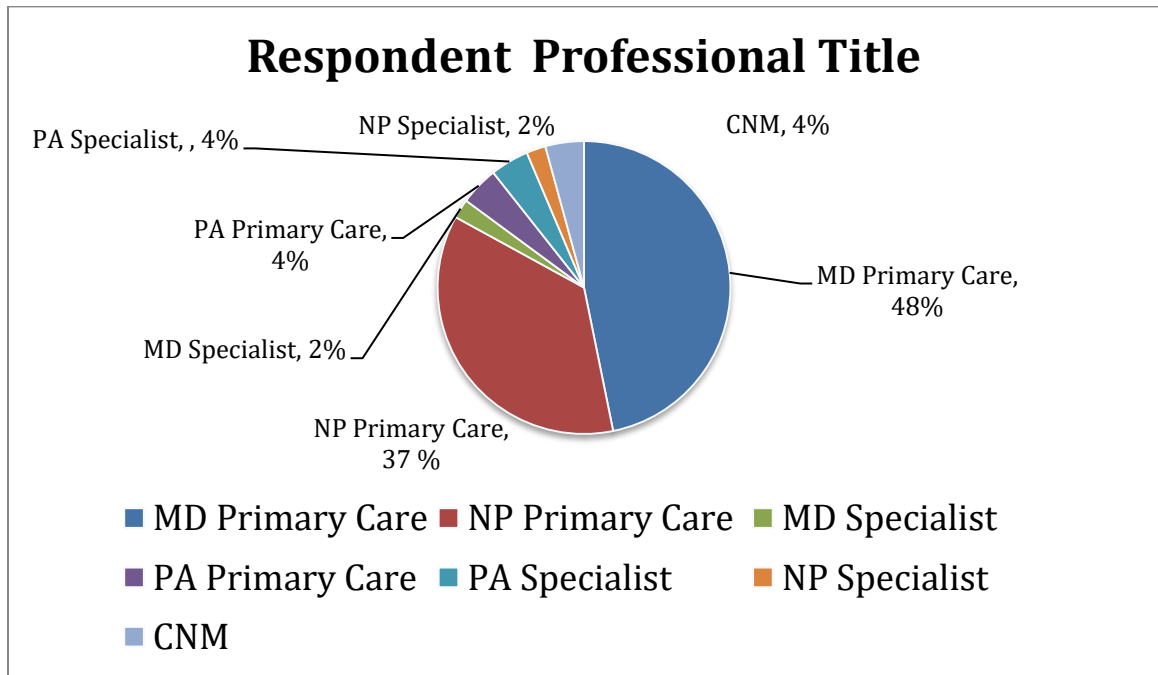
Forty-seven respondents participated in the study. Forty-six respondents met the respondent inclusion criteria (N=46) as described in Chapter 3.

Section Two: Respondent Demographic Information.

Twenty-two respondents (48%) were physicians in primary care (including one DO, an osteopathic physician, one in family medicine, and one in family practice in a reproductive health setting), one was a MD specialist (OB-GYN) (2%), 17 respondents (37%) were NP primary care providers, one respondent was a NP specialist in women's health (2%), two respondents were certified nurse midwives (CNMs) (4%), and two respondents were in PA primary care (4%) and two in PA specialty care (4%). Fifteen respondents (33%) were in practice less than five years. Five respondents (11%) were in

practice five to ten years. Eleven respondents (24%) were in practice ten to 20 years and 15 respondents (33%) were in practice for greater than 20 years. Forty respondents (87%) were female and 6 respondents (13%) were male.

Figure 2. Respondent Professional Title



Section Three: Menopause, Sexuality, and Evaluation of Female Sexual Dysfunction (FSD).

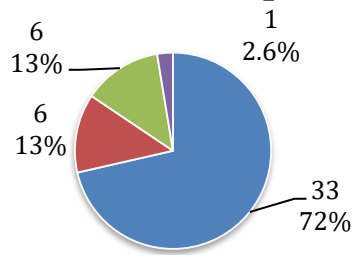
Forty-five respondents (98%) believe that sexuality and sexual satisfaction should be quality of life indicators and perceived that maintaining sexual function is important to the naturally occurring menopausal women that they serve. One respondent (2%) did not answer either question above. Twenty-five respondents (54%) consistently screen naturally occurring menopausal women for sexual dysfunction at each comprehensive health care visit regardless of age, health status, or life circumstances, while 20 (43%) do not. One respondent did not answer (2%).

Section Four: Low Libido and Diminished Sexual Desire in Naturally Occurring Menopause.

Thirty-three respondents (72%) consider low libido and/or diminished sexual desire in naturally occurring menopause to be both a medical condition or disorder and a natural part of aging, while 6 respondents (13%) consider it to be a natural part of aging, and 6 respondents (13%) consider it to be a medical disorder (Figure 3). One respondent did not answer (2%). Twenty-seven respondents (59%) have prescribed a pharmaceutical treatment for naturally occurring menopausal women whose chief complaint was low libido and/or diminished sexual desire, while 18 (39%) have not. One respondent did not answer (2%). Twenty-nine respondents' opinion (63%) was that naturally occurring menopausal women have reported feeling distressed and/or having interpersonal difficulties related to sexual dysfunction in order to receive pharmaceutical treatment for low libido or diminished sexual desire, while 16 (35%) did not. One respondent did not answer (2%). Forty-three respondents (93%) would prescribe a pharmaceutical treatment for a naturally occurring menopausal woman who was otherwise healthy and seeking to maintain her sexual function and enhance sexual satisfaction as long as there were no contraindications and two (4%) would not. One respondent did not answer (2%).

Figure 3. Etiology of Low Libido and Diminished Sexual Desire in Menopause

Etiology of Low Libido and Diminished Sexual Desire in Menopause



- Both a medical condition/disorder and a natural part of aging
- A natural part of aging
- A medical disorder
- No answer

Section Five: Testosterone and Hyposexual Desire Disorder (HSDD).

The respondents were asked to indicate with confidence whether each of the following 11 statements about testosterone were true or false. If the respondent could not answer with confidence, he or she was asked to choose “unable to answer”. Not answering was also an option. This section was designed so that answers chosen to be true reflected a respondent’s accurate knowledge of the statement, while answers chosen to be false represented inaccurate knowledge on behalf on of the respondent. There were a total of 506 truths (most knowledgeable) in section five based on 11 statements and 46 respondents in the study.

Testosterone is not approved by the FDA for HSDD. Nineteen respondents (41%) thought this statement was true while seven (15%) thought this statement was false. Eighteen respondents (39%) were unable to answer with confidence and two respondents (4%) did not answer. Currently, testosterone is not approved by the FDA for low libido or diminished sexual desire.

Sufficient long-term safety and efficacy data is lacking for treatment of HSDD with transdermal testosterone. Twenty-six respondents (57%) thought this statement was true while two (4%) thought this statement was false. Fifteen respondents (33%) were unable to answer with confidence and three (7%) did not answer. According to the FDA and the Endocrine Society, there is insufficient long-term safety data when testosterone is used for this purpose.

According to most studies, testosterone prescribed for HSDD has not been shown to increase the risk or incidence of breast cancer in women. Eighteen respondents (39%) thought that this statement was true and one (2%) thought this statement was false. Twenty-four respondents (52%) were unable to answer with confidence and three respondents (7%) did not answer. Phase three clinical trials have shown that testosterone does not increase the risk or incidence of breast cancer when used for this purpose.

Physiologic doses of transdermal testosterone for women do not increase the risk of heart disease and are not associated with adverse changes to the lipid profile. Eleven respondents (24%) thought this statement was true while ten (22%) did not. Twenty-three respondents (50%) were unable to answer with confidence and two (4%) did not answer the question. Phase three clinical trials have shown that testosterone does not increase the risk or incidence of heart disease and/or changes in the lipid profile when used for this purpose.

According to most studies, testosterone prescribed for HSDD has not been shown to cause endometrial hyperplasia and does not lead to endometrial cancer in women. Fifteen respondents (33%) thought that this statement was true and one (2%)

thought this statement was false. Twenty-seven respondents (59%) were unable to answer the statement with confidence and three (7%) did not answer the question. Studies have shown that testosterone does not cause endometrial hyperplasia and/or endometrial cancer when used for this purpose.

The most common adverse events/side effects reported with use of transdermal testosterone for HSDD are androgenic in nature and dose dependent.

Twenty-five respondents (54%) thought this statement was true and no one thought the statement was false. Nineteen respondents (41%) were unable to answer with confidence and two respondents (4%) did not answer. Along with adhesive site reactions from transdermal patches, the most common side effects reported are androgenic and dose dependent.

Testosterone is the most abundant biologically active female sex hormone in women throughout their lifespan. Ten respondents (22%) thought this statement was true while 12 (26%) thought this statement was false. Twenty-two respondents (48%) were unable to answer with confidence and two (4%) did not answer.

Testosterone is FDA approved for treatment of metastatic breast cancer in menopausal women and hormone-responsive breast cancer in premenopausal women post- oophorectomy. Three respondents (7%) thought the statement was true and 11 (24%) thought this statement was false. Thirty respondents (65%) were unable to answer with confidence and two respondents (4%) did not answer. Testosterone is approved for metastatic breast cancer and in premenopausal women post-oophorectomy especially in cases with metastasis to the bone.

Intra and vulvovaginal testosterone improves symptoms of urogenital atrophy and sexual dysfunction. Ten respondents (22%) thought that this statement was true and nine (20%) thought this statement was false. Twenty-five respondents (54%) were unable to answer with confidence and two (4%) did not answer. In recent studies, testosterone had been shown to improve urogenital atrophy and sexual dysfunction in both women taking aromatase inhibitors and in naturally occurring menopause with age related vaginal complaints.

Testosterone therapy in menopausal women increases the frequency of satisfying sexual activity, sexual desire, and orgasmic response. Sixteen respondents (35%) thought that this statement was true and four (9%) thought this statement was false. Twenty-four respondents (52%) were unable to answer with confidence and two (4%) did not answer. Many studies have proven testosterone's ability to increase the frequency of satisfying sexual activity, sexual desire, and orgasmic response in woman with complaints of low libido and/or diminished desire.

Currently, testosterone therapy for HSDD is contraindicated in women with breast, uterine, and cardiovascular disease. Fifteen respondents (32%) thought this statement was true and one (2%) thought this statement was false. Twenty-eight respondents (61%) were unable to answer with confidence and two (4%) did not answer. According to the Endocrine Society's CPGs, testosterone therapy remains contraindicated in women with breast, uterine, and cardiovascular disease.

Overall, 168 responses (33%) were chosen to be true, 58 responses (12%) were chosen to be false, 255 responses (50%) were unable to be answered with confidence, and 25 responses (5%) were not answered. The average/mean number of truths chosen per

testosterone prescriber was 6.07, while the average/mean number of truths chosen for respondents who have never prescribed testosterone was 2.87 (Figure 5).

Figure 4. Testosterone Knowledge

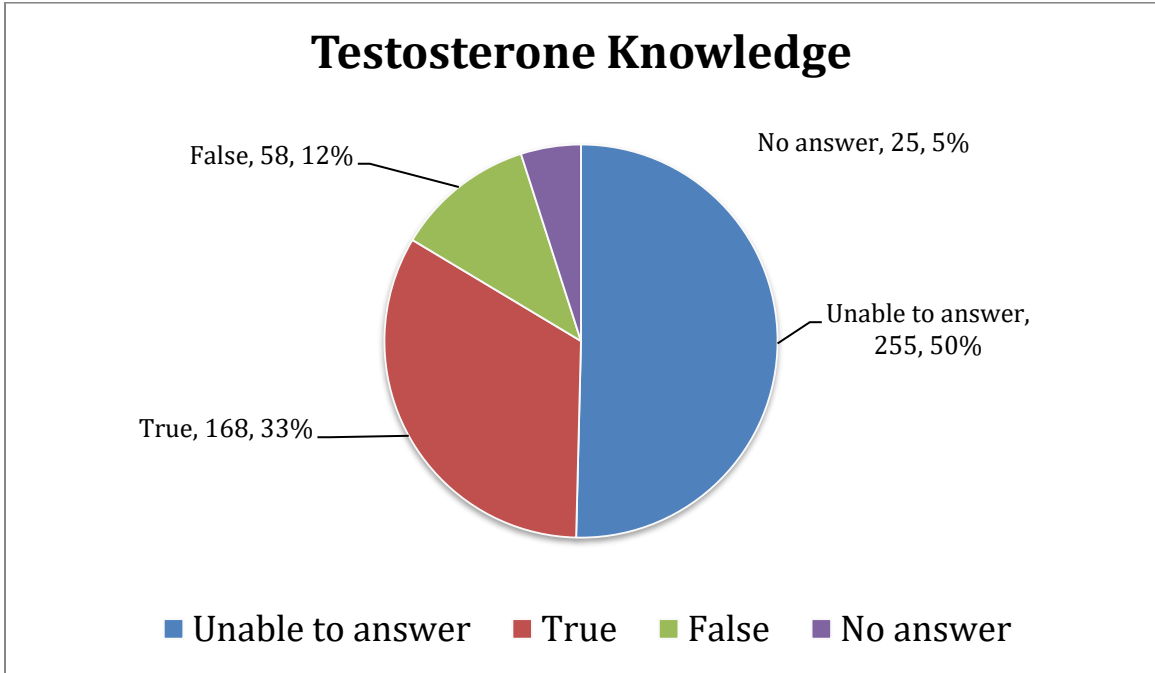
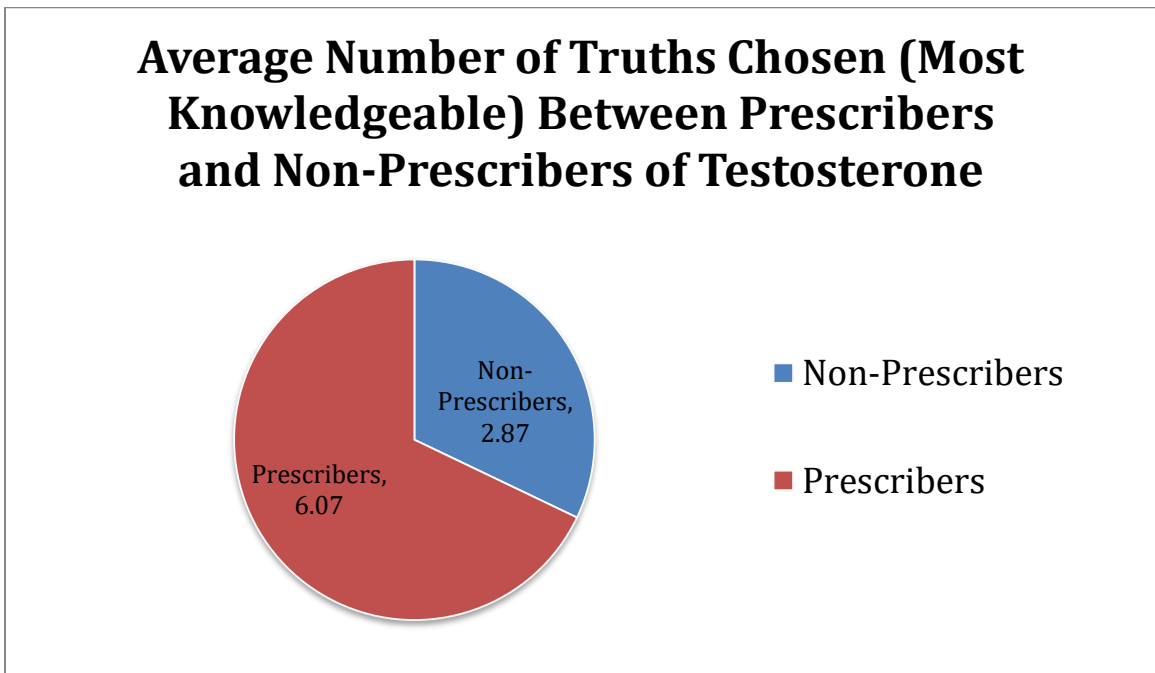


Figure 5. Truths Chosen Between Prescribers and Non-Prescribers of Testosterone



Section Six: Hyposexual Desire Disorder (HSDD) and Clinical practice Guidelines.

Thirty-one respondents (67%) have never prescribed testosterone for naturally occurring menopausal women who sought help for low libido and/or diminished sexual desire and 13 (28%) have prescribed testosterone for this purpose. Forty-two respondents (91%) had not reviewed the updated 2014 clinical practice guidelines (CPGs) set forth by the Endocrine Society regarding androgen/testosterone therapy in women with hyposexual desire disorder while two respondents (4%) have reviewed the guidelines. One respondent did not answer either question (2%).

Additional Statistical Analysis.

Of the 25 respondents who consistently screen menopausal women for sexual dysfunction eight respondents (32%) have prescribed testosterone. Of the 20 respondents that do not consistently screen patients for sexual dysfunction, five respondents (25%) have prescribed testosterone.

Chapter 5: Discussion

Comments

Forty-five respondents (98%), predominately female, believe that sexuality and sexual satisfaction should be quality of life indicators and perceived that maintaining sexual function is important to the naturally occurring menopausal women that they serve regardless of professional title, years in practice, or gender. Further, 43 respondents (94%) would prescribe a pharmaceutical treatment for a naturally occurring menopausal woman who was otherwise healthy and seeking to maintain her sexual function and enhance sexual satisfaction as long as there were no contraindications. Yet, only 25

respondents (54%) consistently screen naturally occurring menopausal women for sexual dysfunction at each comprehensive health care visit.

Interestingly, though the vast majority of respondents acknowledged that menopausal sexuality and subsequently sexual satisfaction and function were important and that they would prescribe a pharmaceutical treatment for healthy women for these purposes, 29 respondents (63%) answered yes to the statement that naturally occurring menopausal women have to report feeling distressed and/or having interpersonal difficulties related to sexual dysfunction in order to receive pharmaceutical treatment for low libido and/or diminished sexual desire. Hence, the respondent's opinions and practices were contradictory in this section. This may reflect the fact that there is not yet a clear stance in the medical literature on what or to what degree constitutes "distress" in relation to a diagnosis of HSDD, and a definition of distress and interpersonal difficulty was not provided to the respondent prior to the questions in this section. Furthermore, the contradictory responses may be related to the confusion and debate over whether low sex drive and low sexual desire in menopause is a medical condition or disorder, a natural part of aging, or both; thirty respondents (65%) consider low libido and/or diminished sexual desire in naturally occurring menopause to be both a medical condition or disorder and a natural part of aging, while 17 respondents (36%) consider it to be a natural part of aging, and eight respondents (17%) consider it to be a medical disorder.

Nevertheless, provider confidence regarding knowledge about research regarding testosterone, a safe and efficacious treatment for HSDD, is lacking. Only 33% of the 11 statements about testosterone were answered accurately, while 12% were answered inaccurately. Approximately half of the respondents (50%) could not answer the 11

statements that tested their knowledge of testosterone with confidence. The majority of the respondents (67%) had never prescribed testosterone for naturally occurring menopausal women who sought help for low libido and/or diminished sexual desire, which may reflect the lack of provider confidence and knowledge regarding testosterone. The results showed that prescribers of testosterone were more knowledgeable about testosterone used for this purpose than non-prescribers. This may indicate that the more knowledge a provider has about testosterone for HSDD, the more likely they are to prescribe testosterone for this purpose than not. Nearly all respondents (91%) had not reviewed the updated 2014 CPGs set forth by the Endocrine Society regarding androgen/testosterone therapy in women with HSDD. Though this is not statistically significant, the two respondents that had reviewed the Endocrine Society's CPGs regarding androgen therapy had prescribed testosterone for menopausal patients complaining of low libido and/or desire.

Conclusions

Providers believe that sexuality and sexual satisfaction are quality of life indicators and perceived that maintaining sexual function is important to the naturally occurring menopausal women that they serve, and the majority of providers would prescribe a pharmaceutical treatment for menopausal women seeking to maintain their sexual function, enhance sexual satisfaction, and/or treat symptoms of HSDD as long as there were no contraindications. However, testosterone is a proven treatment for women with complaints of low libido and/or diminished sexual desire, which was reportedly underutilized for this purpose. This may be related to inconsistent screening for FSD in menopause at each comprehensive visit and lack of provider knowledge about

testosterone (including safety and efficacy) used for this purpose. Further, providers are divided on whether low libido and/or diminished sexual desire in naturally occurring menopause is a medical condition or disorder or a natural part of aging. It is unclear if this impacts evaluation and treatment.

Limitations of the Study

The primary limitation of the study was that the respondent sample size was small. Generalizability was lacking because participation was from Vermont based organizations only. Further, OB GYNs were not well represented in this study. There was an insufficient amount of time to carry out the survey in order to obtain as many respondents as possible and there were no reminders to participate in the study prior to the deadline. The instrument design was inflexible in that most of the questions and answer choices were in a yes or no format. Therefore, the questions that may have been considered controversial or complicated may not have been answered with accuracy and may have been better-represented using alternative data gathering methods such as personal interviews and/or Likert scales. The study instrument tool was not psychometrically tested and while content validity was established, reliability was not. As already mentioned, the meaning of distress was not clearly elucidated in the study, which may have impacted the results.

Suggestions for Further Research

For the PCPs and gynecological healthcare providers who prescribe testosterone for low libido and/or diminished sexual desire, research is needed to assess provider perceptions about the efficacy of the treatment as well as their experiences with being a testosterone prescriber for this purpose. More research is needed to explore

testosterone's role in treating antidepressant induced sexual dysfunction in patients who cannot reduce or discontinue their psychotropic medication. Qualitative research involving personal in depth interviews are necessitated that compare naturally occurring menopausal women's sexual perceptions, feelings, and experiences before and after treatment with testosterone. Additionally, studies are needed to explore the partner's (of the patient prescribed testosterone for low libido and/or diminished desire) perceptions, feelings, and experiences.

Suggestions for Primary Care Practice

Primary care providers and providers of gynecological healthcare must screen menopausal woman for sexual concerns or complaints at every comprehensive visit regardless of age, life circumstances, or medical history with a brief FSD questionnaire (Figure 6). For complaints of low libido and/or diminished sexual desire and/or for the diagnosis of HSDD, transdermal testosterone should be suggested in eligible patients. Furthermore, transdermal testosterone should be suggested for naturally occurring menopausal women who seek to maintain their sexual function and satisfaction in the primary care setting.

Suggestions for the Endocrine Society Regarding CPGs for HSDD

If distress is the hallmark for a diagnosis of HSDD, the Endocrine Society must first define distress in their CPGs for treatment of this disorder. Most importantly, the Endocrine Society must delineate between menstruating women with and without androgen deficiency, surgically menopausal women, and women across the menopausal transition and thereafter in the treatment approach for HSDD with testosterone therapy including routes of administration and dosage. Additionally, the Endocrine Society must

change the tone spoken of this “disorder.” To proclaim that testosterone should not be suggested to “otherwise healthy women” is misleading and clearly does not address the needs of menopausal women with naturally low androgen levels seeking to maintain their sexual function and satisfaction. Lastly, the Endocrine Society must explain why testosterone administration is contraindicated in women with a history of breast cancer when it is approved by the FDA for metastatic breast cancer.

Figure 6. Brief Sexual Symptom Checklist

BRIEF SEXUAL SYMPTOM CHECKLIST

This brief questionnaire can be incorporated into a patient intake form and used as a pre-consultation screening tool (Hatzichristou D, et al. J Sex Med. 2004;1:49-57).

Please answer the following questions about your overall sexual function in the past 3 months or more.

1. Are you satisfied with your sexual function?
 - Yes No If No, please continue.
2. How long have you been dissatisfied with your sexual function? _____
3. The problem(s) with your sexual function is: (mark one or more)
 - a. Problems with little or no interest in sex
 - b. Problems with decreased genital sensation (feeling)
 - c. Problems with decreased vaginal lubrication (dryness)
 - d. Problems reaching orgasm
 - e. Problems with pain during sex
 - f. Other:
4. Which problem (in question 3) is most bothersome (circle) a b c d e f
5. Would you like to talk about it with your health care provider?
 - Yes No

Figure 6. Hatzichristou, D., Rosen, R. C., Broderick, G., Clayton, A., Cuzin, B., Derogatis, L., ... & Sadosky, R. (2004).

Summary

Primary care providers and providers of gynecologic healthcare are in positions to advance sexual health for women in naturally occurring menopause. To do so, leaders in

this arena must help the individual, society, and the medical establishments relinquish stereotypes and embrace a new vision of menopause and sexuality. Leaders can advance sexual health in menopause by embracing the attitude that though menopause signals the end of reproductive capacities, it does not necessarily end a woman's interest in sexual activity or enjoyment. In fact, menopause can be a vital new phase of life with continuation of healthy sexual expression if the patient is interested. Primary care providers and provider of gynecological healthcare can focus on patient-provider communication and patient empowerment through shared knowledge, so that patients can make informed personal choices about their sexual health. One way to advance sexual health for menopausal women is to screen for FSD at every comprehensive visit regardless of patient circumstances and to suggest transdermal testosterone for patients diagnosed with HSDD or for patients merely seeking to maintain sexual dysfunction and satisfaction.

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Appendix A




The
UNIVERSITY
of VERMONT

Committees on Human Subjects
Serving the University of Vermont
and the UVM Medical Center

RESEARCH PROTECTIONS OFFICE
213 Waterman Building
85 South Prospect Street
Burlington, Vermont 05405
(802)656-5040 ph
www.uvm.edu/irb/

Protocol Exemption Certification

TO: Kelly White
FROM: Sarah Wright, Research Review Analyst 
DATE OF CERTIFICATION: 29-Sep-2016
SUBJECT: CHRMS: 17-0150
Transdermal Testosterone for Menopause-Related Hypoactive Sexual Desire Disorder:
Current Guidelines and Provider Perceptions, Knowledge, and Practice

Following IRB review of your project, it has been determined that it qualifies for exemption, as indicated below.

Exemption Category: 2

Federal Exemption: "Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (a) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (b) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation."

This exemption is effective for the duration of the project UNLESS modifications are made that affect the original determination of exemption.

cc: Amy O'Meara

Note: If this project is the study of cancer or is cancer-related, it may require review by the University of Vermont Cancer Center prior to any research activities.

Appendix B
Research Information Sheet

Title of Study: **Sex, Desire, and Menopause!**

Principal Investigator (PI): Kelly White, RN FNP student

Faculty Sponsor: Professor Amy O'Meara, DrNP, WHNP, AGNP

Funder: NA

Introduction

You are being invited to take part in this research study, because you may be a primary care or gynecological healthcare provider for menopausal women. Your participation is very important and will be greatly appreciated! This study is being conducted by Kelly White, RN FNP student and was developed as partial fulfillment of the requirements of the 2016 University of Vermont's Master Science Degree Specializing in Nursing.

Purpose

This is a study of provider perceptions, knowledge, and practice of current practice guidelines for delivering health care to women experiencing hypoactive sexual desire and/or low libido in naturally occurring menopause with a focus on transdermal testosterone.

Study Procedures and Consent

If you decide to take part in the study, the survey can be found on the link/URL address provided in this e-mail located below and is on a secure server through the University of Vermont. This survey **will only take approximately 5-10 minutes of**

your time to complete. Respondents can save partially finished surveys and return to them later. **The survey will only be available through October 28th 2016. You may receive a reminder to take the survey.**

This survey is presented group by group in a multiple-choice and yes/no format.

There are 25 questions divided into 6 groups. The first question is mandatory, because it involves respondent inclusion criteria. After the initial question, you will have the option to not answer any of the other questions in the survey. **By participating in the survey, you are providing consent.**

Benefits and Risks

As a participant in this research study, there may or may not be any direct benefit for you; however, information from this study may benefit other people now or in the future. We will do our best to protect the information we collect from you during this study. We will not collect any information that will identify you to further protect your confidentiality and avoid any potential risk for an accidental breach of confidentiality. If there is an accidental breach of confidentiality, you will be contacted and notified immediately.

Costs and Compensation

There will be no costs to you for participation in this research study. You will not be paid for taking part in this study.

Confidentiality

All information collected about you during the course of this study will be stored without any identifiers (anonymous). No one will be able to match you to your answers.

Anonymity will remain throughout the survey process and thereafter. The respondent

information data provided will be kept separate from the survey questions. No respondent identifying information will be given to the principle investigator conducting this study.

Voluntary Participation/Withdrawal

Taking part in this study is voluntary. You are free to not answer any questions or withdraw at any time. You may choose not to take part in this study, or if you decide to take part, you can change your mind later and withdraw from the study.

Questions

If you have any questions about this study or wish to enquire about the results of this study, please do not hesitate to contact: Kelly White, RN FNP student at (802) 299-7728 (c) or (802) 672-2251 (h). If you have questions or concerns about your rights as a research participant, then you may contact the University of Vermont's Director of the Research Protections Office at (802) 656-5040. Please keep a record of this contact information now. Thank you for your time and cooperation. It is greatly appreciated!

Participation

Your participation is voluntary, and you may refuse to participate without penalty or discrimination at any time. **Please print this information sheet for your records before continuing.**

The link is located at the following URL address:

<https://survey.uvm.edu/index.php/973468?lang=en>

Much appreciation and many thanks,

Kelly White, RN FNP student

Appendix C

Survey Introduction and Questions

The following survey was developed as partial fulfillment of the requirements of the 2016 University of Vermont's Master of Science Degree Specializing in Nursing.

Sex, Desire, and Menopause!

Introduction

This is a study of provider perceptions, knowledge, and practice of current practice guidelines for delivering health care to women experiencing hypoactive sexual desire and/or low libido in naturally occurring menopause.

Please take the time to ensure that your position is represented as accurately as possible. Your response is greatly appreciated and very important! Therefore, please take the time to ensure your position is represented as accurately as possible *without* the use of any references or materials.

This survey will only take approximately 5-10 minutes of your time to complete.

Only the first question is mandatory because it involves respondent inclusion criteria.

You have the option to not answer any of the other questions in this survey. However, if possible, please complete the survey to the best of your ability and answer each question.

There are a total of 24 questions in this survey divided into six groups. You can review your previous answers and make changes as needed prior to submitting the survey.

Much appreciation and many thanks!

There are 24 questions in this survey.

Section One: Respondent Inclusion Criteria

- 1) Are you a primary care provider or provider, a gynecologic health care provider, or a specialty provider who is currently practicing or who has practiced within the last two years with a patient population that includes naturally occurring menopausal females? If NO, please EXIT this survey now. Thank you for your time. Yes or No

Section Two: Respondent Demographic Information

- 1) What is your professional title? Please note your practice specialty in the comment box provided and/or any other professional title not represented in this question. (MD primary care, MD specialty care, PA primary care, PA specialty care, CNM, NP primary care, NP specialty care)
- 2) How many years have you been in practice? <5, 5-10, 11-20, >20
- 3) What is your gender identity? Male, Female, or Other

Section Three: Menopause, Sexuality, and Evaluation of Female Sexual Dysfunction (FSD)

- 1) In general, do you believe sexuality and sexual satisfaction should be quality of life indicators for naturally occurring menopausal women?
- 2) In general, do you perceive that maintaining sexual function is important to the naturally occurring menopausal women that you serve? Yes or No
- 3) In general, do you consistently screen naturally occurring menopausal women for sexual dysfunction at each comprehensive health care visit regardless of age, health status, or life circumstances? Yes or No

Section Four: Low Libido and Diminished Sexual Desire in Naturally Occurring

Menopause

- 1) Do you consider low libido and/or diminished sexual desire in naturally occurring menopausal women to be a medical condition or disorder, a natural part of aging, or both? Medical condition or disorder, A natural part of aging, Both a medical condition or disorder and a natural part of aging
- 2) Have you ever prescribed a pharmaceutical treatment for naturally occurring menopausal women whose chief complaint was low libido and/or diminished sexual desire? Yes or No
- 3) In your opinion, does the naturally occurring menopausal woman have to report feeling distressed and/or having interpersonal difficulties related to sexual dysfunction in order to receive pharmaceutical treatment for low libido or diminished sexual desire? Yes or No
- 4) Would you prescribe a pharmaceutical treatment for a naturally occurring menopausal woman who was otherwise healthy and seeking to maintain her sexual function and enhance sexual satisfaction as long as there were no contraindications? Yes or No

Section Five: Testosterone and Hyposexual Desire Disorder (HSDD)

Please indicate with confidence whether you consider each of the following statements to be true or false. Please do not guess at the answer. Your answers should reflect both your knowledge and perceptions. If you cannot answer with confidence, please mark that you are unable to answer.

1. Testosterone is not approved by the FDA for HSDD.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

2. Sufficient long-term safety and efficacy data is lacking for treatment of HSDD with transdermal testosterone.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

3. According to most studies, testosterone prescribed for HSDD has not been shown to increase the risk or incidence of breast cancer in women.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

4. Physiologic doses of transdermal testosterone for women do not increase the risk of heart disease and are not associated with adverse changes to the lipid profile.

Please choose **only one** of the following:

- True

- False
- Unable to Answer

5. According to most studies, testosterone prescribed for HSDD has not been shown to cause endometrial hyperplasia and does not lead to endometrial cancer in women.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

6. The most common adverse events/side effects reported with use of transdermal testosterone for HSDD are androgenic in nature and dose dependent.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

7. Testosterone is the most abundant biologically active female sex hormone in women throughout their lifespan.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

8. Testosterone is FDA approved for treatment of metastatic breast cancer in menopausal women and hormone-responsive breast cancer in premenopausal women post-oophorectomy.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

9. Intra and vulvovaginal testosterone improves symptoms of urogenital atrophy and sexual dysfunction.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

10. Testosterone therapy in menopausal women increases the frequency of satisfying sexual activity, sexual desire, and orgasmic response.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

11. Currently, testosterone therapy for HSDD is contraindicated in women with breast, uterine, and cardiovascular disease.

Please choose **only one** of the following:

- True
- False
- Unable to Answer

Section Six: Hyposexual Desire Disorder (HSDD) and Clinical practice Guidelines

- 1) Have you ever prescribed testosterone for naturally occurring menopausal woman who sought help for low libido and/or diminished sexual desire? Yes or No
- 2) Have you reviewed the updated 2014 clinical practice guidelines (CPGs) set forth by the Endocrine Society regarding androgen/testosterone therapy in women with hyposexual desire disorder? Yes or No

“It’s okay to talk about birth, okay - then menstruation. I first started my advocacy for women’s health in the field of reproductive freedom, and the next stage would be bringing menopause out of the closet.” Cybill Shepherd