PRIMARY CARE USE OF TESTOSTERONE THERAPY TO BENEFIT WOMEN EXPERIENCING DISTRESS RELATED TO DECREASED SEXUAL DESIRE AFTER SURGICAL MENOPAUSE

by

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Abstract

Testosterone is a biologically significant hormone hypothesized to play a role in supporting women's sexual desire. Women that undergo bilateral oophorectomy experience a marked change in hormonal status including a precipitous decline in testosterone levels. A number of these women experience a corresponding loss of sexual desire which can provoke distress and motivate them to seek sexual health care. Clinical research and guidelines suggest that testosterone therapy may be beneficial in improving sexual desire in these women. However, in Canada there are no licensed testosterone products for women. Consequently, clinicians are required to individually determine how to provide exogenous testosterone therapy. The purpose of this integrative literature review is to provide evidence-informed recommendations, derived from current literature, to inform nurse practitioners practicing in primary care settings how to safely prescribe, monitor and evaluate testosterone therapy. Research and education recommendations are also presented.

Keywords: sexual desire, hypoactive sexual desire disorder, female sexual interest and arousal disorder, nurse practitioner, primary care, testosterone therapy

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Chapter 1: Introduction

The purpose of this integrative literature review was to examine the management of testosterone therapy, and present evidence-informed recommendations, so that nurse practitioners can offer women who are distressed by a decline in their sexual desire, safe and effective care. In particular, the population of interest are women that experience a decline or absence of sexual interest or desire after undergoing a pre-menopausal bilateral oophorectomy for benign indications.

The intersection between sex and health care is exceedingly complex and can be rife with controversy. Especially contentious in both lay and medical communities is the notion of healthy versus pathologic in the context of gender expression, sexual orientation, sexual behaviour, or sexual function (Basson, 2008; Graham, 2016; Hartley, 2006; Moynihan, 2003; Tiefer, 2010). Common medical terminology such as disorder or dysfunction can be controversial, as such terms can be seen to imply that a woman's sexuality is in some way deficient compared to an idealized or presumed norm. Norms that have been predominantly defined by psychiatrists and physicians, may have imposed an unwarranted authority over women's sexuality while failing to acknowledge women's perspectives or those of sexual minority groups (Angel, 2012; Dyer & das Nair, 2013). This criticism is valid; however, many women do suffer distress in relation to their level of sexual function and therefore carefully selected language is warranted in any discussion of these concerns. As such, attention to the use of language that is respectful and free of judgement has been given due consideration within this review. However, I must acknowledge that I may not recognize when my word choice falls short. Terminology such as dysfunction and disorder are used only to reflect the diagnostic language of the published literature and is useful in

communicating the concept that the level of sexual function is such that the woman experiencing it, is distressed by it. There is no intention in use of such language to label or impose a value judgement on a woman's level of sexual function nor to disparage any perspective. The emphasis is on addressing patient-centric concern about diminished or absent sexual desire.

Sexual health care with its myriad facets is different than health care in many other domains. In the evaluation of sexuality there are few objective measures that delineate between normal and pathological and this markedly contrasts with most areas of clinical work where the aim is usually to diagnose a problem according to objective criteria and then treat to rectify the problem. Some sexual health care concerns, such as sexually transmitted infections, lend themselves more readily to the clinical practices of diagnosis and treatment. Although even here, a conscientious practitioner would likely take a holistic approach seeking to gain insight into client specific circumstances that elevate risk, and what education or service might be provided to support better health. While holistic care might not technically be necessary to diagnose and treat a sexually transmitted infection, for instance, other concerns, like lack of sexual interest, always require careful assessment and consideration of a woman's specific values as well as the varied biopsychosocial factors that may contribute to her health experiences (Berry & Berry, 2013; Lamont et al., 2018).

The population central to this integrative literature review is premenopausal women who undergo elective bilateral oophorectomy. Women who undergo bilateral oophorectomies immediately lose the gonadal contribution of sex hormones and undergo an abrupt surgically induced menopause (Davis & Wahlin-Jacobsen, 2015). Sex hormones are biologically important to sexual function in both the central nervous system, and in

peripheral tissues (Davis & Wahlin-Jacobsen, 2015). Although there is not a manifest universal decline in sexual desire and responsiveness associated with oophorectomy, a significant number of women, particularly younger women premenopausal prior to surgery, complain of diminished sexual interest or responsiveness, and meet the criteria for the medical diagnosis of sexual desire dysfunction (Davis & Wahlin-Jacobsen, 2015; Lamont et al., 2018; Sayim et al., 2018). Meta-analyses of clinical studies have concluded that exogenous testosterone with and without concurrent estrogen can effectively treat sexual desire concerns (Achilli et al., 2016; Somboonporn, Bell & Davis, 2010). Despite studies conducted without concurrent estrogen therapy, the current standard of care for premenopausal women that undergo hysterectomy with oophorectomy for benign conditions is that they receive estrogen replacement at least until the average age of natural menopause, around fifty-one years old (Siyam et al., 2018). Estrogen replacement in this population not only reduces menopausal symptoms, but is seen to reduce risk of osteoporosis and related fractures, vulvovaginal atrophy and dyspareunia, and is associated with less cardiovascular disease, atherosclerosis, impaired cognition and dementia (North American Menopause Society 2017 Hormone Therapy Position Statement Advisory Panel, 2017). Perhaps most informative in this topic area is the analysis of the Nurses' Health Study cohort, which has shown that elective oophorectomy before the age of 50, without estrogen therapy, is associated with a 40% higher risk of death from all causes (Parker, 2014).

In relation to testosterone, the positive conclusions reached in sexual desire studies are reflected in guideline support for therapeutic trials of exogenous testosterone in postmenopausal women distressed by diminished sexual desire and meeting the other criteria for sexual desire dysfunction (Lamont et al., 2018; Shifren & Gass, 2014; Wierman

et al., 2014). Despite guideline support for the use of exogenous testosterone in this population of patients, there are no approved testosterone formulations for women in North America (Lamont et al., 2018). Even with burgeoning interest in treating sexual dysfunction with testosterone, there is little practical information for how to implement, manage, and evaluate a testosterone trial in women (Jayasena, Alkaabi, Lievers, Handley, Franks & Dhillo, 2019). The lack of practice guidance is problematic as research has shown that, despite holistic intent, few health care providers engage proactively in sexual health care due in large part to a lack of practicable knowledge (Dyer & das Nair, 2013). As a result of this integrative literature review, provided to nurse practitioners are evidence-informed recommendations from current scientific literature, on the use of testosterone therapy in women who have undergone a premenopausal oophorectomy, and have subsequently been diagnosed with low and distressing levels of sexual desire. First, the paper presents background and context to key considerations regarding the research question: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause? Second, a description of the literature search methodology is provided. And third, findings extracted from the selected literature, are synthesized and discussed, with implications related to practice recommendations included.

Chapter 2: Background and Context

In this background chapter key concepts are examined in order to provide context from which literature search findings and recommendations can be evaluated. These include 1) sexual function, 2) sexual response models, 3) controversy surrounding the sexual dysfunction label, 4) defining sexual dysfunction, 5) the production and action of

testosterone in women, 6) testosterone deficiency, 7) surgical menopause, 8) efficacy of testosterone therapy, 9) selection of patients for therapy, 10) prescriber considerations surrounding off-label prescription and compounding, 11) communicative therapeutic relationships, and 12) sexual health care knowledge acquisition.

Sexual Function

Sexual function is an important facet of the human experience. Sexual function is complex and diverse, spanning from the basic mechanics necessary for procreation to enabling personal expression in pursuit of physical pleasure, intimacy, and psychological satisfaction. Sexual function is important to the quality of life of most individuals, and when function falters it can diminish the quality of life of the affected person as well as introduce challenges to interpersonal sexual relationships (Clayton & Valladares Juarez, 2017; Shifren et al., 2000). In medical literature the absence of function is referred to as dysfunction, and sexual dysfunction refers to the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish (World Health Organization [WHO], 2006). The WHO (2006) states that sexual health is not merely the absence of dysfunction, disease, or infirmity, it is a condition of well-being in body, mind, and social functioning with regard to all aspects of sexuality, thereby enabling the possibility of pleasurable and safe sexual experiences. Sexual interest or desire are important elements of sexual function, and sexual function is a component of sexual health.

Sexual response models. Sexual function has long been studied, and the last century marked the publication of large epidemiological studies that attempted to establish the parameters of normal human sexual function (West, Vinikoor, & Zolnoun, 2004). Researchers such as Masters, Johnson, Kaplan, Hite, Kinsey, and Lief are well known for

their research into sexuality and sexual function during this timeframe. Masters and Johnson's book Human Sexual Response published in 1966 is a seminal publication that detailed their understanding of the human sexual response cycle (HSRC). Masters and Johnson's HSRC model has served as the foundation for decades of sexuality research (Graham, 2016). The HSRC model presents a linear conceptualization of sexual response with stages corresponding to excitement, plateau, orgasm, and resolution (Basson, 2000). The HSRC model has remained largely unchanged since the mid 1970s when Helen Kaplan further stratified Masters and Johnson's excitement phase into desire and arousal, thus denoting that sexual desire precedes the other phases; see Figure 1 (Kingsberg & Rezaee, 2013). Although recent literature has challenged the eminence of the HSRC model, it remains widely accepted as the de facto model of sexual response and has served to underpin the definitions for aberrance of sexual function (Balon & Clayton, 2014; Graham, 2016).

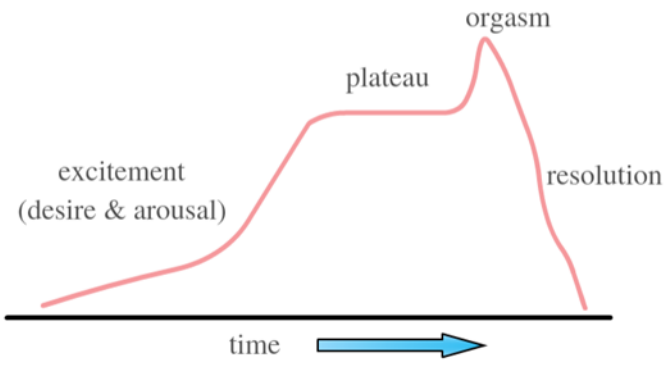

Figure 1. Illustration of linear progression of human sexual response per the concepts of the HSRC model.

Despite its widespread acceptance, the HSRC has many detractors who state the model may do an adequate job of explaining male sexual response but does not have the

sophistication to model the complexities of female sexual function, especially in the realm of desire and arousal (Basson, 2000, 2008). More complex models of female sexual response, for example, Basson's circular model, have recently come to prominence, and this has had profound impact on the conceptualization of normal female sexual function (Graham, 2016).

One of the key differences between the linear HSRC model and a circular model is how sexual interest or desire are conceptualized. In the HSRC model it is postulated that sexual desire is an innate appetite that motivates a person to engage in sexual activity, whereas the circular model proposed by Basson does recognize some spontaneous desire but places much more emphasis on the responsive nature of a woman's desire; see Figure 2 (Basson, 2000).

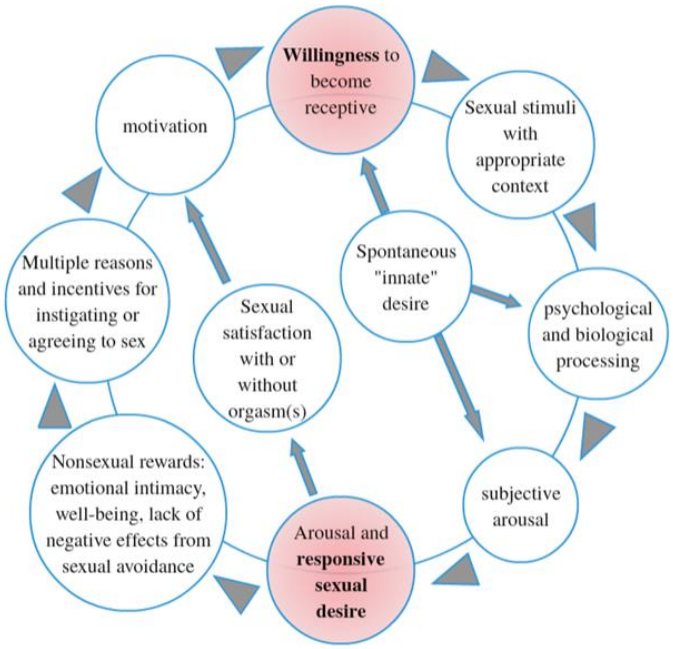

Figure 2. Illustration of Basson's circular model of responsive sexual desire that begins from a state of sexual neutrality, but with a willingness to become receptive. From "Women's Sexual Dysfunction: Revised and Expanded Definitions" by R. Basson, 2005, *Canadian Medical Association Journal, 172,* p. 1328. Copyright 2005 by Canadian Medical Association. Adapted with permission.

Basson's model proposes that instead of a biological urge, women's motivation "stems from a number of 'rewards' or 'gains' that are not strictly sexual, these rewards being additional to, and often of far more relevance than, the women's biological neediness or urge" (Basson, 2000, p. 52). Basson argues that this reconceptualization of women's sexual response changes the way that women's sexual function should be assessed. Recognition of a circular female sexual response cycle that is different than the linear model and focusses more on receptivity to sexual cues serves to de-pathologize the experience of many women with low spontaneous desire (Basson, 2000). This newer model steers assessment away from an urge and genital focus to one that focusses on a woman's perception of her sexual function (Graham, 2016).

Controversy over the label of dysfunction. A long-standing critique of the concept of female sexual dysfunction is that the terminology is rooted in the medical model and represents patriarchal and psychiatric hegemony over women's minds, bodies and behaviours (Angel, 2012; Tiefer, 2010). Further, there is stigma associated with the credence that sexual dysfunction is a manifestation of serious psychopathology (Angel, 2012; Lamont et al., 2018).

In the early 2000's, further concern developed around the terminology "female sexual dysfunction" (FSD). FSD became more polarizing, garnering much criticism that it is a non-specific disease state fabricated by those aligned with pharmaceutical industry interests, in order to pathologize the sexual function of millions of women. This was viewed as creating a market for female sexuo-pharmaceuticals that might rival the multi-billion dollar-per-year market of phosphodiesterase type 5 (PDE5) inhibitors like Viagra for male erectile dysfunction (Moynihan, 2010; Tiefer, 2010). Moreover, these scholars contend that

a pseudo-feminist rhetoric of sexually empowering women has been employed (Moynihan, 2010; Tiefer, 2010).

Laumann, Paik and Rosen (1999) reported a 43% prevalence of sexual dysfunction in women 18 to 59 years old. Although this figure of 43% is often cited in sexual dysfunction literature, it also receives a good deal of criticism from many authors, including Moynihan (2003) and Tiefer (2010) as a gross overestimate that pathologizes mild and transient sexual function problems that are sufficiently common as to be considered normal. Arguments contend that the reductionist medicalization of female sexuality, and judging sexual diversity against narrow genital function-oriented definitions, only serve to disproportionately emphasize biological determinants that may be amenable to pharmaceutical influence; while ignoring the psychological and social determinants that may actually be more powerful predictors of sexual function (Moynihan, 2010; Tiefer, 2010). The consternation is perhaps understandable given that the gold standard for treatment of sexual dysfunction over the previous decades has been the biopsychosocial (BPS) model; and addressing the psychosocial elements has historically been preeminent, as few medications are available (Berry and Berry, 2013).

As the biopsychosocial nomenclature indicates, this model asserts that sexual function is dependent on the complex interplay of biological, psychological, social-interpersonal, and social-cultural elements (Berry & Berry, 2013). However, since the incredible success of PDE5 drugs there has been a determined search for a female analogue, a ‘pink Viagra’ estimated to be worth billions of dollars annually (Hartley, 2006). Feminist authors such as Tiefer and Hartley lament the capital expenditure on finding the next blockbuster molecule, rather than supporting initiatives like sexual education that may go

further to helping women achieve healthy sexual function (Moynihan, 2010; Tiefer, 2010). Despite these thought-provoking criticisms, medical research conducted over the 20 years since the advent of Viagra, has expanded the knowledge base about biologic pathways in female sexual function, leading to pharmacologic innovation. As an example, in 2018 Health Canada licensed Addyi (flibanserin), the first medication approved for treatment of female sexual dysfunction in premenopausal women by either Health Canada or the Food and Drug Administration (Health Canada, 2018; Food and Drug Administration, 2015).

Defining sexual dysfunction. The Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association (APA) has long provided a system for classifying sexual dysfunction, and provides criteria to establish a clinical diagnosis. Since the first version was published in 1952, subsequent versions or major revisions were published in 1968, 1980, 1994, 2000 and 2013 (Graham, 2016). Influential work by Kaplan, and Harold Lief in the mid 1970s led to the inclusion of inhibited sexual desire disorder as a diagnosis in DSM-III (Segraves & Woodard, 2006). Each iteration of the DSM has made changes reflecting evolution in the psychomedical understanding of sexual behaviours; and an espoused goal in the latest publication was to narrow the focus of diagnosis so to curtail over diagnosis (Graham, 2016). The DSM is widely used in diagnosing dysfunction and has defined sexual dysfunctions as "a group of disorders that are typically characterized by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure" (APA, 2013, p. 423). With DSM-5, published in 2013, female sexual dysfunction is described in three different domains: sexual interest/arousal disorder, orgasmic disorder, and genito-pelvic pain/penetration disorder (APA, 2013). Where DSM-IV contained four domains of female

sexual dysfunction, the DSM-5 working group controversially combined the DSM-IV categories of hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder to create a new broader diagnosis of female sexual interest/arousal disorder (FSIAD) (Balon & Clayton, 2014). This disrupts the parallelism that existed between the male and female sexual dysfunction diagnoses, and the diagnoses are no longer based on the linear HSRC model (McCabe et al., 2016).

An expressed goal of the working group was to "raise the bar" of the diagnostic criteria so that women experiencing temporary or even adaptive change in their sexual desire would not be diagnosed with a sexual disorder (Graham, 2016, p. 38). This goal seems to acknowledge some of the criticisms leveled about the over diagnosis of FSD. Further, to accommodate an acknowledged greater diversity in normal sexuality, stringent criteria were developed and two morbidity criteria, symptom duration and severity, were added to the definition (Graham, 2016; Mitchell et al., 2016). Additionally, the nature of the distress required, in order to diagnose FSIAD relative to HSDD, changed from "marked distress or interpersonal difficulty" to "clinically significant distress in the individual" (Graham, 2016, p. 40). This change made the diagnosis more patient-centric, in that the distress is as experienced by the individual rather than possibly being defined by discordance of desire in a relationship or the distress experienced by a partner (Graham, 2016).

Controversially, there are authors that state that distress should not be a criterion at all; as other diagnoses, for example diabetes, heart disease, or cancer, do not require a person to be distressed in order to be diagnosed (Brotto, 2010; Spitzer & Wakefield, 1999). However, it is countered that asexuality without distress does exist, and may be considered a sexual identity rather than a sexual dysfunction (Brotto, 2010). Pathologizing individuals

that do not wish to be sexual would be to continue the unfortunate imposition of dogma that pathologizes homosexual and gender diverse populations. Therefore, while distress may not be important to some clearly pathologic diagnoses, the very personal nature of sexuality requires that personal distress is an essential criterion (Graham, 2016).

In a European study it was shown that rates of low sexual desire after surgical menopause were similar amongst women from four different countries, thereby suggesting biological influence (Graziottin, Koochaki, Rodenberg, & Dennerstein, 2009). Despite this, distress due to the low sexual desire, and consequently the diagnosis of HSDD, varied by country; thereby suggesting a role for cultural factors, which highlights the need to interpret low desire in relation to the experience of sexual distress (Graziottin et al., 2009). Perhaps problematic is that there is no consensus on what constitutes "clinically significant distress," and this terminology is not further clarified in the DSM (Spitzer & Wakefield, 1999). Spitzer and Wakefield in their examination of the concept propose that clinically significant distress means "a level of severity in intensity, duration, or other relevant dimension that is marked or substantial" (p. 1858); and in their critique it is acknowledged that the concept is ultimately reliant on clinical judgement and subsequently open to interpretation.

In recognition that there is an enormous variation in women's experiences of sexual arousal and desire, the DSM-5 working group developed a polythetic criterion A, and three other criteria that must be met in order to diagnose FSIAD (Graham, 2016). The four diagnostic criteria (A,B,C,D) for FSIAD are shown in Table 1. O'Loughlin, Basson and Brotto (2018) found that the new FSIAD criteria do in fact raise the bar for diagnosis which allows identification of women with more severe forms of dysfunction rather than mild or transient symptomology that does not warrant a diagnosis of a sexual disorder.

Table 1

DSM-5 Criteria for Female Sexual Interest/Arousal Disorder

A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following: 1. Absent/reduced interest in sexual activity 2. Absent/reduced sexual/erotic thoughts or fantasies 3. No/reduced initiation of sexual activity and typically unreceptive to a partner's attempts to initiate 4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts) 5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g. written, verbal, visual) 6. Absent/reduced genital or non-genital sensations during sexual activity in almost all or all (75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts)
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months
C. The symptoms in Criterion A cause clinically significant distress in the individual
D. The sexual dysfunction is not better explained by a non-sexual mental disorder or as a consequence of severe relationship distress (e.g. partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Note. Adapted from American Psychiatric Association, 2013*, Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (5th ed.). Copyright 2013 by the American Psychiatric Association.

Dueling Definitions, Continuity of Literature and Impact

The revised diagnoses and diagnostic criteria in DSM-5 impacts the continuity of research literature for female sexual dysfunction and "creates havoc in the entire area of sexual dysfunctions" (Balon & Clayton, 2014, p. 1227). Even recently there have been calls to revert to implementing HSDD criteria rather than FSIAD (Goldstein et al., 2017; Parish et al., 2016). Perhaps more controversial than reversion, is the development of new definitions during the fourth International Consultation on Sexual Medicine (ICSM) in 2015. The authors recognized that there may be a real disservice in having multiple partially conflicting or overlapping definitions in the field of sexual health, as it can impact the certainty that

findings from different researchers or locations will be applicable to other patient populations (McCabe et al., 2016). Despite this, the ICSM recommendation was still to create a hybrid system that incorporates definitions from DSM-5, DSM-IV-TR, and the WHO International Classification of Diseases, 10th edition (ICD-10), in order to arrive at "the most accurate and contemporary definition" (McCabe et al., 2016, p. 139). Further confusing matters, the ICSM definition related to desire uses the same acronym, HSDD, but term it hypoactive sexual desire dysfunction rather than disorder (McCabe et al., 2016).

Most published prevalence surveys or therapeutic studies over the past 25 years concerning FSD were conducted using the diagnostic criteria for HSDD in DSM-IV (Balon & Clayton, 2014). Therefore, literature that informs about prevalence or treatment of HSDD has to be reinterpreted in light of the new diagnostic criteria. In the literature, there is debate and speculation as to the impact of the changes, with some authors contending that many women with HSDD will suffer harm, as they may no longer qualify for treatment coverage under the new diagnostic criteria for FSIAD (Balon & Clayton, 2014; Graham, 2016). However, a recent study has perhaps added some clarity as it found that 73.5% of women diagnosed with HSDD, also meet the criteria for FSIAD (O'Loughlin et al., 2018). Consequently, it might be acceptable to estimate the prevalence of FSIAD as roughly three-quarters of the historic prevalence data for HSDD.

In terms of the treatment literature, it is also challenging to know how to utilize HSDD data to inform treatment of FSIAD. However, if as O'Loughlin et al. (2018) propose, FSIAD represents a subset of more symptomatic HSDD, and if the hypothesis of testosterone deficiency causing low sexual desire in women who have had an oophorectomy is indeed correct, it is reasonable that testosterone therapy, efficacious for HSDD, would

confer benefit in FSIAD. There is some support in the literature for this conclusion. The International Menopause Society suggests in their 2016 recommendations that because testosterone therapy has been demonstrated to improve both sexual desire and arousal, women diagnosed with the new composite FSIAD should be managed as women previously diagnosed with HSDD (Baber, Panay, Fenton, & IMS writing group, 2016). Although this assertion appears to be logically consistent, it may not be correct. Consequently, even five years after the introduction of FSIAD criteria, a number of physicians continue to exclusively use HSDD criteria for diagnosis and treatment due to validated research, tools, and a history of clinical utility (Clayton, Kingsberg & Goldstein, 2018).

In this project, when citing research specific to HSDD or FSIAD, the appropriate terminology is used. In other discussion, that could refer to either diagnosis, terminology such as "a condition of low sexual desire" is used.

Testosterone

Testosterone therapy for sexual function in surgically menopausal women is not a new concept. Since the late 1930's it has been recognized that testosterone has a positive effect on women's sexual desire (Triash, Guay, Spark & Testosterone Therapy in Women Study Group, 2007). This spurred a decade of research into the effects of testosterone on women's sexual function, and as early as 1948 research literature had reached consensus on testosterone's enhancement of women's libido (Traish et al., 2007). In 1943, Salmon and Geist (as cited in Traish et al., 2007) postulated that testosterone has "a three-fold action in women: (i) to increase the susceptibility to psychosexual stimulation; (ii) to increase the sensitivity of the external genitalia; (iii) to increase the intensity of sexual gratification" (p. 1224). Despite these positive findings testosterone was not used therapeutically for women's

sexual function and research trailed off for decades until renewed interest was sparked by the commercial success of Viagra (Traish et al., 2007).

Testosterone is often referred to as the ‘male sex hormone’, yet testosterone is the most abundant biologically active hormone in women (Glaser & Dimitrakakis, 2015). In women, testosterone circulates at higher concentrations than the quintessential “female sex hormone” estradiol (Davis, Worsley, Miller, Parish & Santoro, 2016). Not only is testosterone itself a critical hormone in female physiology, but all endogenous estrogens are synthesized from testosterone via aromatization (Glaser & Dimitrakakis, 2015).

Testosterone is a molecule in the class of C19 steroids, termed androgens, which includes androstenedione (A4), dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS), and 5-α-dihydrotestosterone (DHT) (Bachmann et al., 2002). Production of testosterone and other androgens is stimulated by luteinizing hormone and adrenocorticotropic hormone via the hypothalamic-pituitary-gonadal-adrenal axis, but the feedback loop that moderates production in women has not been described (Bachmann et al., 2002; Davis & Wahlin-Jacobsen, 2015).

Testosterone levels in females vary throughout the lifespan, both longitudinally with age, as well as cyclically with diurnal and menstrual variations (Davis & Wahlin-Jacobsen, 2015). Testosterone levels start to rise in females around the age of 6-8 years, following the maturation of the adrenal zona reticularis, marking the onset of adrenarche (Davis and Wahlin-Jacobsen, 2015). At menarche the ovaries produce cyclical surges of testosterone coinciding with ovulation and levels remain elevated during the luteal phase (Rothman, Carlson, & Xu et al., 2011). Peak lifetime levels of testosterone are seen in women in their 20s and 30s followed by a slow but steady decline, that does not appear to vary with the

natural menopause transition, and reaches a nadir in a woman's early 60s (Davis & Wahlin-Jacobsen, 2015; Davison, Bell, Donath, Montalto & Davis, 2005).

In women, testosterone is produced in the ovaries, and the adrenal glands, as well as at the cellular level (Bachmann et al., 2002). The ovaries and the adrenals release testosterone and androgen precursors A4 and DHEA into the blood stream, whereas the precursor DHEAS is almost exclusively released by the adrenals (Shifren & Davis, 2017). Prior to menopause, approximately 50% of circulating testosterone comes from the ovaries with the remainder coming from the adrenals and the peripheral conversion of the main pre-androgens A4 and DHEA (Davis et al., 2016). Sixty to sixty-five percent of testosterone in the blood stream is tightly bound to sex hormone binding globulin (SHBG), 30% to 40% is associated with albumin or corticosteroid binding globulin (CBG), and only 2% of testosterone exists in a free state (Davis et al., 2016; Demers, 2010). Only free testosterone, and the fractions that are relatively weakly bound to albumin or CBG are considered bioavailable (Demers, 2010). Complicating quantification of the bioavailable fraction of testosterone are significant fluctuations in SHBG levels that can vary widely for many reasons, including estrogen levels (endogenous, hormonal contraceptives, or hormone replacement), cortisol, dietary habits, obesity, thyroid disorders, diabetes, liver and renal disease (Demers, 2010). Further complicating accurate quantification is that, an indeterminate amount of testosterone is produced in the target tissue itself from androgen precursors, and only a very small portion of this intracrine testosterone leaks back into the blood stream to be measured (Basson, 2008).

Testosterone is widely biologically active either directly via interaction with androgen receptors, or indirectly via active products such as dihydrotestosterone or estradiol

(Davis and Wahlin-Jacobsen, 2015). Testosterone effects central nervous system pathways in the hypothalamus and limbic system, as well as peripheral sites such as breast, bone, skeletal muscle, adipose tissue, and genital tissue (Bachmann et al., 2002). Testosterone has favorable effects on vascular endothelial function and vascular tone, and some studies suggest women with lower testosterone may be at higher risk for coronary heart disease events (Davis & Wahlin-Jacobsen, 2015). Endogenous testosterone is neuroprotective, and a functional MRI trial has shown exogenous testosterone can preserve cognitive function, as well as subtly but significantly improve verbal learning and memory in post menopausal women (Davis et al., 2014). Further, clinical evidence points to roles for testosterone in sexual desire, mood, energy and psychological well-being (Bachmann et al., 2002; Davis & Wahlin-Jacobsen, 2015).

Testosterone mechanisms of action. The mechanisms by which testosterone influences sexual desire in women remain unknown (Cappalletti & Wallen, 2016; Davis et al., 2016; Traish et al., 2007). It is hypothesized that there are both central and peripheral effects of sex hormones that support sexual desire. At the genital level testosterone either directly, or indirectly through aromatization to estradiol, helps support the vitality, sensitivity, lubricity, and function of vaginal and clitoral tissues (Archer, Love-Geffen, Herbst-Damm, Swinny, & Chang, 2006; Cappalletti & Wallen, 2016). This may indirectly increase sexual desire through making sexual intercourse more pleasurable (Cappalletti & Wallen, 2016). At the level of the brain, functional MRI has shown that exogenous testosterone and estradiol cross the blood-brain barrier and interact with receptors throughout the CNS where they increase global brain activation to erotic stimuli, particularly in the limbic system (anterior cingulate gyrus, amygdala, hypothalamus and thalamus)

(Archer et al., 2006). Sex hormones may play a role in tipping the balance by potentiating sexual excitatory pathways, or modulating inhibitory pathways in the brain, as proposed in the dual control model (Bancroft, Graham, Janssen & Sanders, 2009).

A contemporary criticism of the studies in the 1940's was that women were receiving "shockingly supraphysiological amounts of testosterone" in order to demonstrate sexual function benefit (Cappalletti & Wallen, 2016, p.4). Renewed research into testosterone and female sexual function began in the mid 1980's, and a randomized placebo-controlled trial published by Shifren et al. in 2000 is considered a landmark study (Panzer and Guay, 2009). As opposed to supraphysiologic doses of testosterone, Shifren et al. (2000) used physiologic doses of transdermal testosterone to demonstrate an improvement in sexual function, and psychological well-being in a population of women with impaired sexual desire after oophorectomy.

Testosterone deficiency. It is evident that testosterone is an important hormone in women's physiology and health. Yet, there is a great deal of controversy around the concept of a female androgen deficiency disorder (Demers, 2010). In part, this stems from the historic emphasis of testosterone's role in virilization, masculinity, and male sexual function (Bachmann et al., 2002; Demers, 2010). But also, there has been limited technical capability to accurately quantify testosterone levels at normal physiologic female concentrations (Demers, 2010; La'ulu, Kalp, & Straseski, 2018). Analytical methods have long been optimized to deliver relatively precise measurement at male physiologic levels, which are roughly 10 to 20 times higher than the levels found in women (La'ulu et al., 2018; Moal, Mathieu, Reynier, Malthiery, & Gallois, 2007). Consequently, correlations between clinical

states and blood levels of testosterone have been challenging to demonstrate because of inaccuracy in analytical measurements (Davis et al., 2016).

Standardization and accreditation of analytical methods in clinical laboratories coupled with use of more sensitive techniques, such as gas chromatography and mass spectrometry (GC/MS) in clinical studies, have now begun to show correlations that were previously indiscernible (Davis et al., 2016). For example, where previous studies were unable to conclusively demonstrate a correlation between levels of free testosterone and sexual desire, more recent research has shown statistically significant correlation between androgen levels and sexual desire, including frequency of masturbation which is described as a compelling metric of intrinsic sexual desire because it is partner-independent (Shifren & Davis, 2017; Wahlin-Jacobsen et al., 2015). Despite these findings of correlation, Wahlin-Jacobsen et al. (2015) state that, due to the multifactorial nature of sexual desire, complex endocrine, paracrine and intracrine pathways, menstrual variation, and genetic polymorphisms of androgen receptors, there is no role for using blood testosterone levels to help diagnose sexual desire problems. There is no identifiable threshold of testosterone below which sexual function is consistently impaired, nor is there a cut-off level that identifies candidates for testosterone therapy (Davis et al., 2016). In short, a circulating testosterone level is of limited value as an indicator of sex steroid action or sexual function (Davis et al., 2016).

Surgical Menopause

Hysterectomy has been a mainstay treatment for abnormal uterine bleeding and pelvic pain for more than 100 years, and is second only to caesarian section in terms of surgical procedures undergone by Canadian women (Schaffer & Word, 2002; Stankiewicz,

Pogany, & Popadiuk, 2014). In the US, peak incidence of hysterectomy is when a woman is in her forties, which is also the peak period of sexual activity in women's lives (Elsamra et al., 2010; Merrill, Layman, Oderda, & Asche, 2008). Of particular relevance for this review is that according to US statistics around 55% of women that undergo hysterectomy receive a concurrent bilateral oophorectomy (Parker, 2010). Oophorectomy may be performed to address a malignant or benign ovarian condition, or it may be performed at the time of a benign hysterectomy to reduce the risk of ovarian cancer, or it may be performed as a prophylactic measure in women with a genetic predisposition to breast or ovarian cancer (Siyam et al., 2018). Historically, there was belief that all women who receive a hysterectomy after the age of 40 should have an oophorectomy to reduce their risk of ovarian cancer (Parker, 2010). Rates of concurrent oophorectomy vary by age: 3% of women 18-30, 48% of women 31-50, 77% of women 51-64, 68% of women older than 65 (Sharma & Schumann, 2009).

Hysterectomy as a therapeutic modality for benign disease has declined by up to 40% over the last several years with an increased use of medical therapies such as levonorgestrel intrauterine systems, and conservative procedures such as uterine artery embolization, and endometrial ablation to treat benign uterine illness (Moorman et al., 2011; Thakar, 2015). Yet, despite these changes in therapeutic approach, tens of thousands of hysterectomies are still performed in Canada each year. Canadian Institute for Health Information (CIHI) (2018) data for 2016-2017, report that across Canada 41,841 women received a hysterectomy. Although British Columbia has the lowest rate of hysterectomy per 100,000 population, 5,201 women in B.C. had a hysterectomy in 2016/17 (CIHI, 2018). If

B.C. statistics for concurrent oophorectomy are similar to those in the US, thousands of women in B.C. undergo oophorectomy each year.

Oophorectomy, testosterone and sexual function. Although hysterectomy halts menstruation, this does not represent hormonal menopause without concurrent oophorectomy. That said, hysterectomy alone has been associated with lower levels of circulating sex hormones in women, likely attributable to damage to the ovarian vascular supply (Davison et al., 2005). Oophorectomy in premenopausal women unequivocally results in hormonal menopause, referred to as surgical menopause. In the 1970s and 1980s there was recognition that surgical menopause is correlated with reduction of sexual desire, but at the time this was attributed to "a psychogenic response to the loss of an important symbol of femininity" (Nappi, Wawra, & Schmitt, 2006, p. 319). It is postulated by some authors, that the precipitous fall of estrogens and androgens produced by the ovaries, results in a loss of sexual thoughts, and a diminished capacity to respond to cues or triggers that would have previously elicited sexual desire (Basson, 2000). A study by Leiblum, Koochaki, Rodenberg, Barton, and Rosen (2006) found that after surgical menopause women between the ages of 20 and 49 were significantly more likely to experience low sexual desire than their premenopausal counterparts.

As mentioned, testosterone levels in women naturally vary throughout the lifespan. By her 40s, a premenopausal woman's serum testosterone is 50% lower than in her 20's (Archer et al., 2006). Women who have undergone bilateral oophorectomy see an additional 50% decrease in their testosterone levels within 24 hours of surgery due to loss of the ovarian contribution of sex hormones (Bachmann, 2001; Braunstein, 2002). Interestingly, the substantial between-women variation of testosterone levels with age means that an

androgen profile will not reliably differentiate between naturally and surgically menopausal women (Wierman et al., 2014). The surgical menopause resultant from oophorectomy in premenopausal women results in a level of estradiol that is similar to levels seen in naturally menopausal women, but significantly lower levels of testosterone, as even after natural menopause the ovaries continue to produce about 50% of circulating testosterone as the adrenal contribution tapers from 25% to 10% (Pluchino et al., 2013).

The prevalence of clinically significant sexual desire concerns in any population is difficult to estimate as it varies according to the data collection approach, including sample selection, variations in definitions, time span measures, interview technique, and survey instruments used (Brotto, 2010; Mitchell et al., 2016). In terms of women who have undergone an oophorectomy, Leiblum et al. (2006) found that 36% of surgically menopausal women experienced low sexual desire, but not all of these women experience distress associated with their low levels of desire. Other studies estimate that women under the age of 45 had the highest prevalence of distress related to low levels of sexual desire, with 20% to 26% reporting distress (Lamont et al., 2018). With a combination of low sexual desire, and corresponding distress, this group of women experiences symptoms outlined in HSDD and FSIAD diagnostic criteria.

The abrupt change in a woman's hormonal milieu with surgical menopause has been known for decades, and prompted numerous studies to discern the relationship between sexual function and testosterone levels (Sherwin, Gelfand, & Brender, 1985). Research has found that despite estrogen replacement, women who have undergone oophorectomy experience a greater decline in sexual function than women who undergo natural menopause and this spurred research into testosterone replacement in women who experienced surgical

menopause (Sherwin et al., 1985). Sherwin et al. conducted a prospective trial and found that women that had undergone oophorectomy for benign conditions reported higher levels of sexual desire, arousal, and fantasies when they received testosterone alone or testosterone-estrogen preparations compared to estrogen alone or placebo.

Efficacy of Testosterone Therapy

Since Sherwin et al.'s research, particularly in the early 2000s, women who had undergone oophorectomy prior to natural menopause were a popular study population, serving as a testosterone deficient model in an attempt to demonstrate that low levels of endogenous testosterone impaired sexual function and that restoration of testosterone to premenopausal physiologic levels improved sexual function (Cappalletti &Wallen, 2016; Panzer & Guay, 2009). Several well-designed placebo-controlled trials of testosterone replacement have shown significant improvements in domains of sexual function in surgically menopausal women (Huang et al., 2013; Kingsberg & Rezaee, 2013).

Although some individual studies failed to demonstrate efficacy, the majority of studies demonstrate similar effects of efficacy on sexual function regardless of type of menopause, duration, or location of the study (Davis & Shifren, 2017; Somboonporn et al., 2010). The efficacy is not only limited to statistically significant improvements in sexual desire, but also includes significant improvements in: number of satisfying sexual events, orgasm number and intensity, blood flow to genital tissue, responsiveness, sexual self-image, sexual relationship satisfaction, and decreased personal distress scores (Achilli et al., 2016; Davis et al., 2016; Elraiyah et al., 2014; Hubayter & Simon, 2009; Somboonporn et al., 2010; Wierman et al., 2014). It is worth noting that efficacy might not emerge for 6-8 weeks, peaks and plateaus after 3 months of therapy, and that therapeutic trials should end

after 6 months if a woman is experiencing no benefit (Davis et al., 2016; Shifren & Davis, 2017; Wierman et al., 2014).

Despite positive conclusions of statistical improvement with testosterone plus estrogen compared to estrogen alone, the effect size remains relatively modest. For example, the average increase of satisfying sexual events, which is the primary endpoint required by the FDA to demonstrate efficacy in the treatment HSDD, was 1-2 per month (Shifren & Davis, 2017). However, other metrics such as a subjective report of a meaningful treatment benefit (52% treatment vs 31% placebo), or a reduction in personal distress (65-68% treatment vs 40-48% placebo) do show larger effect size (Elraiyah et al., 2014; Shifren & Davis, 2017; Wierman et al., 2014). Some authors contend that these subjective measures of improvement are more important than objective counts of SSEs (Hubayter & Simon, 2008; Kingsberg & Althof, 2011; Pyke & Clayton, 2018; Shifren & Davis, 2017). In the reviewed literature there is little discussion of how efficacy should be evaluated in the primary care context outside of clinical trials. Clinical trials have predetermined lengths, use survey tools to discern small differences in effect, and predetermine a suite of safety outcomes to evaluate, but how to adapt clinical trial methodology to appropriate primary care practice remains uncertain.

Selecting Patients for Testosterone Therapy

Many authors indicate that choosing the right patients for testosterone therapy is challenging (Davis et al., 2016; Elraiyah et al, 2014; Hubayter & Simon, 2008; Panzer & Guay, 2009; Somboonporn et al., 2010; Wierman et al., 2014). Although the most recent studies show there is moderate correlation between serum testosterone levels and sexual desire, sexual desire remains subjective and there are no identifiable testosterone cut-offs or

other objective measures that can be used to diagnose sexual desire dysfunction (Davis et al., 2016; Somboonporn et al., 2010). Even when a woman presents with sexual distress consistent with a diagnosis of a sexual desire disorder, testosterone therapy may not be an appropriate therapy (Hubayter & Simon, 2008; Lamont et al., 2018). This holds true even for women who have undergone a bilateral oophorectomy and therefore have a greater likelihood of having low endogenous testosterone levels (Panzer & Guay, 2009; Shifren & Davis, 2017; Wierman et al., 2014). Even amongst this group of women, who arguably have the most compelling presentation to justify exogenous testosterone supplementation, the multifactorial context dependent complexities of sexual desire may mean that contributors, other than low testosterone levels, are more pertinent and need to be addressed first (Lamont et al., 2018; Shifren & Davis, 2017; Somboonporn et al., 2010).

Testosterone therapy may be appropriate as part of the treatment plan for a woman distressed by her lack of sexual desire, but decisions need be made on a case-by-case basis and individualized to the woman's values and preferences (Elraiyah et al., 2014; Lamont et al., 2018). Evaluation of potential contributors such as quality of the interpersonal relationship, life stress, fatigue, thyroid disease, hyperprolactinemia, vaginal atrophy, vulvodynia, dyspareunia, vasomotor symptoms, and depression should all be considered and any biological or psychological factors not attributable to endogenous testosterone levels should be treated prior to prescription of testosterone therapy (Hubayter & Simon, 2008; Panzer & Guay, 2009; Shifren & Davis, 2017). Even if psychological or other physical factors do not seem to be contributory to the diminished level of sexual desire, non-pharmacologic interventions such as reducing fatigue and stress, optimizing physical health, varying sexual routines, and improving relationship quality and communication, may

improve desire and obviate the need for pharmacotherapy (Hubayter & Simon, 2008; Lamont et al., 2018; Shifren & Davis, 2018). The long-term risks of testosterone therapy are currently unclear, so exploring non-pharmacologic interventions prior to testosterone therapy is clinically prudent (Shifren & Davis, 2018). If desire and responsiveness still do not improve, a trial of testosterone therapy can be considered along with the continued integration of psychosocial solutions, and this may lead to better outcomes (Davis et al., 2016; Lamont et al., 2018; Shifren & Davis, 2017; Wierman et al., 2014).

There is extensive debate whether a condition of low sexual desire is a significant and clinically relevant problem or if the concept of sexual desire dysfunction has been medicalized only to create a target population for a profitable pharmaceutical market (Biddle et al., 2009; Moynihan, 2003; Tiefer, 2010). Despite the debate, Biddle et al. (2009) conclude that women with HSDD experience impairments in their quality of life that can be similar in magnitude as women living with back pain or diabetes. For the majority of women sexual health is an undeniable part of their sense of self and sexual dysfunction is disruptive to emotional health and relationships (Kingsberg & Rezaee, 2013). The importance of sexual health is recognized by practitioners that see psychosocial determinants as the most relevant to sexual function and those that seek to find solutions through pharmacologic means. This reiterates the value of applying the biopsychosocial model in treatment of distressing levels of sexual desire. Operationalizing the BPS model by addressing psychosocial parameters, and providing pharmaceutical support, might allow practitioners to help women achieve what they really want. Which according to Dr. McHugh, a human sexuality psychologist, is “better, more affectionate relationships, fulfilling consensual

sexual relations, more time and energy for the expression of sexual desires, acceptance and acknowledgement of female sexual desire, and more sex education" (McHugh, 2006, p.361).

Support for Testosterone Prescription

In Canada, support for a primary care provider role in managing testosterone therapy comes from the Society of Obstetricians and Gynecologists of Canada guidelines on female sexual health that recommend that health care providers should provide care to women with hypoactive sexual desire rather than referring them, even if this means seeking collaboration with an interdisciplinary team (Lamont et al., 2018).

The relative consensus in medical literature surrounding moderate efficacy of testosterone for HSDD has led to guideline support for trials of testosterone in women with HSDD if other contributing criteria such as relationship issues are not identified (Lamont et al., 2018). A recent taskforce appointed by the Endocrine Society, American Congress of Obstetricians and Gynecologists, American Society for Reproductive Medicine, European Society of Endocrinology, and International Menopause Society endorses trials of testosterone as do the Society of Obstetricians and Gynaecologists of Canada, and the North American Menopause Society (Lamont et al., 2018; Shifren & Gass, 2014; Wierman et al., 2014). The endorsements from these societies are for conservative trials in select patients, for example women distressed by a change in libido following oophorectomy (Korkidakis & Reid, 2017). Although the recommendations are cautious, they are characterized by the respective authors as level one recommendations, indicating good and consistent scientific evidence (Shifren & Gass, 2014).

Although the increase in satisfying sexual events per month is modest, the changes have been statistically significant, and women have reported clinically meaningful benefit

(Kingsberg & Rezaee, 2013). Systematic reviews and meta-analysis of these trials confirm the efficacy of testosterone treatment and despite not knowing the mechanism for testosterone's efficacy, guideline recommendations suggest trials of testosterone treatment when no other identifiable biopsychosocial factors better explain the decline in sexual interest and arousal (Achilli et al., 2016; Elraiyah et al. 2014; Lamont et al., 2018; Somboonporn, Bell & Davis, 2010). Despite these recommendations, there are no licensed formulations of testosterone for women in either Canada or the United States (Petering & Brooks, 2017).

A large pharmaceutical company, Procter & Gamble, presented trial data on the efficacy of transdermal testosterone to the FDA in 2004 in hopes of having a transdermal testosterone patch approved for market (Basaria & Dobs, 2006). Despite the FDA panel voting 14 to 3 recognizing testosterone's efficacy in the treatment of female hypoactive sexual desire, the panel did not approve the application due to lack of long-term safety data (Basaria & Dobs, 2006). Consequently, testosterone therapy for women necessitates off-label prescribing of testosterone products licensed and intended for men, or tailored compounded products (Petering & Brooks, 2017). Numerous authors, those in favour of testosterone therapy and those opposed, recognize that off-label prescription of testosterone is not ideal (Davis & Worsley, 2014; Hartley, 2006; Nappi, 2015; Tiefer, 2010).

Off-label Prescription and Compounding

As stated, there are no approved testosterone therapies, for treating women's sexual function, in Canada or the United States (Clayton et al., 2018). Despite this, thousands of women a year receive off-label prescriptions of testosterone, predominantly due to distress over low libido (Nappi, 2015; Snabes & Simes, 2011). A US survey in 2009 estimated that

more than 4 million prescriptions for testosterone were written off-label for women, and another estimate claims at least 20% of all testosterone gel sales are to women (Amato & Buster, 2009; Snabes & Simes, 2011). These large numbers are due to the fact that women seek care for reduced sexual desire, there is guideline support for testosterone use for select women with HSDD, and there are no licensed products (Nappi, 2015; Petering & Brooks, 2017).

Off-label prescription of pharmaceuticals is the practice of prescribing a medication for an indication or population other than the indication and population verified and authorized by Health Canada (Canadian Agency for Drugs and Technologies in Health [CADTH], 2015). A 2012 study in Canada showed an 11% prevalence of off-label prescription by primary care physicians (Eguale et al., 2012). The most common circumstance was prescribing medications to populations of patients that were not included in the research submitted for evaluation by Health Canada (Eguale et al., 2012).

Any prescription of testosterone to women in North America constitutes off-label prescribing. Some critics of off-label prescription of testosterone to women for sexual function suggest that the practice is inherently risky, and a surreptitious way for the sex drugs industry to circumvent the stringent approval process for medications by the FDA or Health Canada (Hartley, 2006; Tiefer, 2010). In line with their argument, there is literature to support the increased risk of adverse events when drugs are used off label; however, when there is strong scientific evidence, defined as at least one randomised controlled study, adverse events were the same for on-label use (CADTH, 2015; Eguale et al., 2012; Eguale et al., 2016).

In terms of testosterone therapy for women, it is not as straight forward as prescribing an existing approved medication for women for a new indication of sexual function concerns. The only commercially manufactured products available are for men. However, the approved gel, foam, or cream products in packets or pumps, or transdermal patches for hypogonadal men, are around 10 times more potent than the correct dosing for women, making safe usage challenging (Davis and Worsley, 2014). Consequently, there has been an enormous growth in prescribing compounded testosterone at concentrations more appropriate for female use (Davis & Worsley, 2014). Compounding of medication presents a challenge to current pharmaceutical best practices (Sellers & Utian, 2012).

Historically, before the advent of commercial manufacturing of pharmaceuticals, doctors and pharmacists created formulations of drugs according to the needs of their patients, and their own knowledge of medicopharmacy (Sellers & Utian, 2012). Compounding was widely practiced, but this gave way to prescribing and dispensing of standardized drug products that were rigorously evaluated, manufactured under stringent controls, and approved by federal authorities (Sellers & Utian, 2012). In Canada, the Food and Drugs Act, and Food and Drug Regulations govern the manufacture of drugs, and the compounding of medications must also comply with all relevant sections of the Food and Drugs Act (Health Canada, 2009). However, the manufacture of brand name or generic drugs is subject to federal oversight and regulation, and the compounding of medications is overseen and regulated by the provincial/territorial pharmacy regulatory bodies (College of Pharmacists of British Columbia [CPBC], 2018; Health Canada, 2009). As such, compounded medications are subject to less regulatory oversight and have been associated with quality defects such as contaminants and variations in potency and bioavailability

(Gass et al., 2015; Sellers & Utian, 2012). In fact, substantial published research, and bodies such as the Institute for Safe Medication Practice Canada (ISMP-Canada), have identified significant issues with the quality of compounded medications (Gass et al., 2015; Grober et al., 2015; Kawano & Ho, 2012; Sellers & Utian, 2012). Grober et al. (2015), in a study of ten randomly selected compounding pharmacies in Toronto, reported that significant inaccuracy existed within and between pharmacies, in the compounding of testosterone gels and creams. Fewer than half of all samples tested within ± 20% of the prescribed dose, whereas the accepted standard is ± 10%, or within the range of 90.0% to 110.0% (Allen, Bassani, Elder, & Parr, 2015; Grober et al., 2015).

In 2009, pursuant to its mandate to promote drug safety, Health Canada produced a policy document on the manufacture and compounding of drugs in Canada, in order to ensure consistent and appropriate regulation (Health Canada, 2009). Building on this policy, and utilizing resources such as the United States Pharmacopeia, frameworks have been developed to address quality issues with compounded medications (ISMP-Canada, 2017; National Association of Pharmacy Regulatory Authorities [NAPRA], 2018). ISMP-Canada has worked with NAPRA to inform the creation of Model Standards to be adopted by the respective provincial pharmacy regulatory authorities (ISMP-Canada, 2017; NAPRA, 2018). These standards, coupled with the accompanying guidance documents, provide comprehensive direction, and set the minimum requirements that need to be met in order to ensure the safety of patients and compounding personnel (NAPRA, 2018). In support of continued access to personalized strengths and dosages of medications, while meeting a threshold standard of safety and quality, the College of Pharmacists of B.C. is committed to implementing the NAPRA standards (CPBC, n.d.). With the implementation of these Model

Standards, nurse practitioners will be able to have a higher degree of confidence that the compounded medications they prescribe are compounded according to sound pharmaceutical practices. However, research will be required to determine if these standards facilitate quality improvement such that compounded medications begin to match the consistent quality associated with licensed commercially-manufactured pharmaceuticals (Grober et al., 2015).

Nurse practitioners in British Columbia have the authority to prescribe many drugs, including off-label and compounded medications subject to the standards, limits and conditions set by the British Columbia College of Nursing Professionals (BCCNP) (BCCNP, 2018a). However, in terms of prescription of testosterone therapy, nurse practitioners must also meet the BCCNP standards, limits, and conditions for prescribing controlled drugs and substances (CDS) (BCCNP, 2018a). The BCCNP lists the requirements for CDS prescription on their website which includes additional specified education, meeting employer requirements, adherence to the NP Scope of Practice, and PharmaNet access (BCCNP, 2018b). As with the prescription of any medication, nurse practitioners are accountable for the prescribing decisions that they make. They must use current evidence in their decision making, and must be competent to establish a diagnosis, manage the treatment, and monitor the client's response to the prescribed drug (BCCNP, 2018a).

Communicative Therapeutic Relationships

One of the guiding principles of NP practice is the provision of service within a holistic model of care (BCCNP, 2018a). A holistic imperative necessitates assessment of health in all domains, including the domain of sexual health. Holistic inquiry about sexual health, and the cultivation of rapport, help create a therapeutic relationship in which women

are more comfortable speaking about sexual concerns (Kingsberg & Knudson, 2011). Not only does inquiry about sexual health legitimize sexual health as a permissible subject to talk about, and present an opportunity for a woman to acknowledge a current troublesome issue, but it also demonstrates an NP's willingness to engage in care about issues that are more sensitive in nature (Higgins, Barker & Begley, 2006). This assurance can dispel the commonly held patient belief that care providers do not have the time for, or interest in, sexual health matters, or that the provider is embarrassed by discussion of sexual concerns (Berman et al., 2003; Odey, 2009). Initiation of conversation can be as simple as asking for permission, or inviting the patient, to discuss any sexual concerns (Higgins et al., 2006; Odey, 2009). When an NP assesses for sexual health concerns, this aligns well with many women's preference that their primary care provider broach the topic of sexual health; further, women that have primary care providers that have previously enquired about sexual difficulties are far more likely to seek medical help for a sexual concern (Gott, Galena, Hinchliff & Elford, 2004; Higgins et al., 2006; Laumann. Glasser, Neeves, & Moreira, 2009; Odey, 2009). The ability to foster a communicative therapeutic relationship in regards to sexual health might be especially important as there are relatively few objective measures in sexual health; and determination of patient goals, as well managing treatment, requires open communication (Lamont et al., 2018).

Sexual Health Care Knowledge Acquisition

Despite a philosophical grounding and practice approach that may benefit NP practice in sexual health, there is concern expressed by women's health leaders, and others, that few NP education programs provide adequate preparation for sexual health care competence (Auerbach et al., 2012; Berg et al., 2014; Cappiello, & Nothnagle, 2013;

Simmonds, Hewitt, Aztlan, & Skinner, 2017; Taylor et al., 2014; Quallich, 2014). The Canadian context of sexual health education is challenging to discern from literature, as there is a paucity of published information regarding sexual health education and training in Canadian NP programs (Sheinfeld, Arnott, El-Haddad, & Foster, 2016). In their survey of Canadian NP programs, Sheinfeld et al. conclude that there is uneven and inadequate coverage of reproductive health issues. Medical curricula are similarly critiqued, and suggestions for improving sexual health education across all health disciplines include improving education in the key areas of knowledge, skills, and attitudes through blended learning modalities incorporating multidisciplinary exposure and improved evaluations of student performance (Shindel, Baazeem, Eardley & Coleman, 2016). While NPs bring key assets of compassion, empathy, and non-judgement to patient care, it is recognized that knowledge about sexual medicine must often be gained through self-directed learning undertaken by providers that value the importance of sexual health to the overall well being of women (Dahir, 2011).

The purpose of this capstone project was to undertake an integrated literature review, in order to present evidence-informed recommendations for managing testosterone therapy in women, who after having undergone a premenopausal bilateral oophorectomy for benign conditions, have subsequently sought care for concerns around decreased sexual desire and meet criteria for the diagnosis of a condition of low sexual desire. Thus, my research question is: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause? In the following section, the methodology employed in answering this research question are presented.

Chapter 3: Methods

In the creation of this project I have utilized the methodology presented by Whittemore and Knafl (2005) for integrative literature reviews. This kind of review allows for the collation of data from a variety of published sources and has been described as "research of research" (Whittemore & Knafl, p. 548). Whittemore and Knafl describe a method to increase the rigour and reduce the risk of bias when analyzing and synthesizing from diverse sources of literature in order to articulate the state of the science and provide recommendations that comprise evidence-informed practice. Whittemore and Knafl state that after the clear identification of the research question, a well-defined and comprehensive literature search needs to be undertaken. This chapter describes the process of my literature search.

There has been exponential growth in published scientific literature on female sexual arousal and desire over the past 20 years (Graham, 2016). Consequently, the initial database searches returned hundreds of results and it was challenging to sort through the volume of papers in order to decipher which papers were relevant and which where extraneous to answering my research question. I created a concept map, shown in Figure 3, to help define my search terminology; and this aided me in narrowing search returns to articles more pertinent to answering my research question: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause?

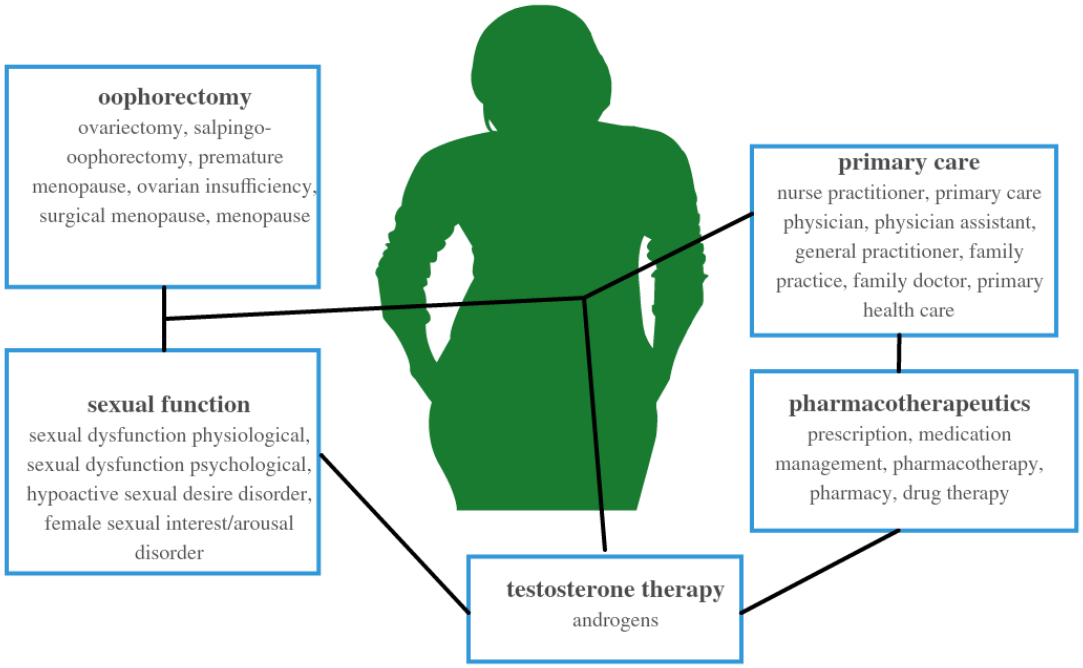

Figure 3. Concept map created to aid literature search.

I had limited success in finding appropriate articles in my database searches when executing searches using terminology from all of my individual groupings. For example, the stipulation of primary care or other synonyms consistently reduced my search results to zero. I found better success when searching without the primary care qualifier, and determined that the primary care term is not necessary as literature supports the fact that testosterone prescription is part of primary care services (Petering & Brooks, 2007). In fact, Petering and Brooks (2007) state that primary care providers write more than half the prescriptions for testosterone therapy in the United States. I decided that by not stipulating primary care as a search term, I appropriately avoided the problem of incurring too few search results. I then applied inclusion or exclusion criteria to narrow down the larger field of results.

Specifying oophorectomy or similar words such as ovariectomy also significantly limited my search results. Many search results were limited to the early to mid 2000's and I obtained relatively few results of literature published more recently. I suspect this reflects the evolution of research foci at different times. Women who had undergone oophorectomy were an ideal early study population due to their low levels of endogenous testosterone, and a number of clinical trials were conducted from 2000 through to 2006. However, testosterone and sexual function research shifted to naturally menopausal women in the late 2000s, and most recently to the study of premenopausal women. I found that including the term menopause instead of oophorectomy proved useful as searches produced more recent articles for review.

In September 2018, I conducted searches of the Medline, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PubMed databases. In Medline and CINAHL I utilized medical subject headings (MeSH) when they were suggested, and I also exploded any MeSH that had the option to do so. Exploded MeSH are denoted with a '+' in the table below. Exploding the MeSH allowed retrieval of articles indexed to the MeSH term, as well as indexed to narrower subject terms. I used the Boolean operators OR and AND to generate the results list in each database. I used filters to limit results to English language articles and specified a date range from 2000 to 2018. Appendix 1 contains my search terms and database results. The search results from the three databases were exported to EndNote Web in order to remove duplicate articles, leaving 172 unique articles.

I developed inclusion and exclusion criteria shown in Table 2 in order to systematically work through the literature search results. This led to narrowing down the

body of literature to a select group of articles to be analyzed in order to answer my research question.

Evaluation of article quality was challenging as the results constitute a diverse spectrum of literature from lay-person opinion articles to meta-analyses. However, the completion of a comprehensive search and evaluation of published literature in the article methods sections, along with perceived informational value to answer my research question, guided the determination of key inclusion criteria. Quality was also assessed using Critical Appraisal Skills Programme (CASP) checklists, particularly the systematic review checklist as it was the most appropriate for the review articles selected.

Table 2

Inclusion and Exclusion Criteria

Inclusion criteria:	• surgical menopause for benign conditions • sexual function (desire/arousal/interest) • physiological concentration testosterone replacement • route of administration • informed consent • comprehensive analysis conducted • favorable assessment per CASP criteria	• menopause • testosterone • dose • monitoring • safety • key informational value • concurrent estrogen therapy
Exclusion criteria:	• male • transgender • other medications for sexual function including combinations with testosterone (except estrogen) • oophorectomy after menopause • oophorectomy for malignancy • non-sexual-function benefits of testosterone	• supraphysiologic testosterone • pre-menopause • dyspareunia • anorgasmia • vulvovaginal atrophy

After screening titles and abstracts using the inclusion and exclusion criteria, there were 34 remaining articles. Full-text review of these articles allowed further narrowing of the field. However, with review of reference lists, and select searches using Google Scholar and PubMed, I found some key articles not included in my original database searches. This was not unexpected as Whittemore and Knafl (2005) state that, due to limitations associated with database searching, one might expect a database search to provide about 50% of eligible studies and that, ancestry searching, networking, purposive sampling and hand searches are also recommended to access relevant literature. Further full-text review selection allowed me to narrow my select literature to a group of 11 articles by using my inclusion and exclusion criteria. These articles, a collection of systematic reviews and meta-analyses, guidelines, literature reviews, and a safety extension study, comprise my literature for this integrative literature review. Figure 4 shows a Prisma Flow Diagram of my search.

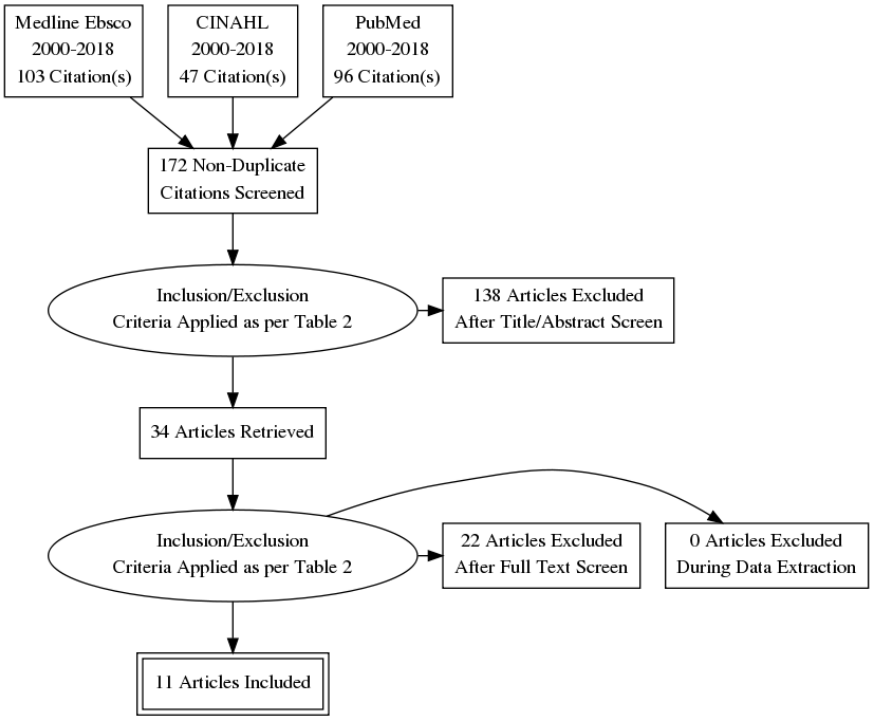

Figure 4. Prisma Flow Diagram of Literature Search.

The following chapter presents findings after extraction of data from the articles, and identification of themes in the literature that provide answers to facets of my research question.

Chapter 4: Findings

The purpose of this integrative literature review was to answer the question: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause? The eleven articles selected through the literature search and review process detailed in the methods section were examined in detail and data was extracted and organized. The selected works comprise of three systematic reviews and meta-analyses (Achilli et al., 2017; Elraiyah et al., 2014; Somboonporn et al., 2010), two guidelines (Lamont et al., 2018; Wierman et al., 2014), five literature review articles (Al-Imari & Wolfman, 2012; Davis et al., 2016; Hubayter & Simon, 2008; Panzer & Guay, 2009; Shifren & Davis, 2017), and one open label extension study of safety (Nachtigall et al., 2011). Each article was evaluated for: 1) aim, 2) study design and location, 3) sample, methods and analysis, 4) authors' key findings, 5) auxiliary findings, and 6) strengths and limitations. After extraction of the data, the work was further analyzed to identify themes, patterns, and relationships as described by Whittemore and Knafl (2005). In this chapter, evidence-informed practices begin to manifest as findings from the literature are presented. In the next chapter, Discussion and Implications for Practice, findings are synthesized, occasionally with auxiliary literature to address a few evident gaps, so to present evidence-informed practice recommendations on the management of testosterone therapy.

Themes from the Literature

Nurse practitioner standards of practice in B.C. mandate the use of current evidence to support decision making, and accountability for all prescribing decisions an NP makes (BCCNP, 2018a). This directive influenced my reading of the assembled literature and prominent themes of therapeutic efficacy, proper patient selection, and therapeutic safety were identified. My research question is situated amongst these prominent themes. Considerations pertaining to the demonstrated efficacy of testosterone therapy, and patient selection for this therapy, are contextual to my research question, and thus have been reviewed in the background and context chapter of this integrative literature review. While the evidence of testosterone's efficacy and appropriate patient selection are preamble to my research question, therapeutic safety is a critical theme that informs the management of testosterone therapy. After having determined that a woman is an appropriate candidate for testosterone therapy, safety considerations guide many further decisions. The theme of therapeutic safety is broad, and the literature highlights many facets including: known and potential adverse effects, relevance to informed consent, routes of administration, appropriate dosing, monitoring and assessment of therapy, and considerations of off-label use.

Safety of Testosterone Therapy

After extracting data from the literature, it is evident that exploration and evaluation of safety is a major thematic emphasis in all of the selected articles. This is understandable given the powerful roles of hormones in influencing biological action. Supplemental exogenous testosterone is thought to exert its influence via androgen receptors, which are widespread throughout the body (Somboonporn et al., 2010). Additionally, it is possible that

exogenous testosterone, aromatized to estradiol, exerts influence via the widespread estrogen receptors (Somboonporn et al., 2010). Accordingly, with so many potential sites of action among varied body systems, a wide variety of potential risks have been evaluated in clinical trials and observational studies (Davis et al., 2016). Studied safety outcomes include: breast cancer, breast pain, endometrial cancer, cerebrovascular events, cardiovascular events, androgenic effects, lipid levels, liver function, renal function, blood pressure, plasma viscosity, coagulation parameters, hematology, body mass, carbohydrate metabolism parameters, fasting glucose, insulin sensitivity, diabetes, headaches, migraines, anxiety, and emotional lability (Achilli et al., 2016; Al-Imari & Wolfman, 2012; Davis et al., 2016; Elraiyah et al., 2014; Hubayter & Simon, 2008; Lamont et al., 2018; Nachtigall et al., 2011; Panzer & Guay, 2009; Shifren & Davis, 2017). Despite this long list of studied outcomes, a consistent critique in the articles is that the body of scientific literature contains limited long-term data, and most data is extracted from trials of 24 months or less (Al-Imari & Wolfman, 2012; Davis et al., 2016; Shifren & Davis, 2017; Somboonporn et al., 2012). Consequently, uncommon adverse events, or potential adverse events that require longer exposure to testosterone therapy, cannot be fully evaluated in the current body of literature (Nachtigall et al., 2011). To date, testosterone therapy has been evaluated in phase 1 (safety and dosage), phase 2 (efficacy and side effects), and phase 3 (efficacy and monitoring of adverse reactions) clinical trials (Clayton et al., 2018; FDA, 2018). Phase 3 trials, often known as pivotal trials, typically last between 1 and 4 years, sometimes allowing detection of long-term or rare side effects (FDA, 2018). Success in phase 3 often leads to approval by regulatory agencies (FDA, 2018). This demonstrates that the evidence compiled for testosterone therapy is in line with many approved medications.

Androgenic side effects. At physiologic levels, few adverse effects signaled safety issues at a higher rate in testosterone groups than in the comparison groups, with the only significant signals being mild acne and hirsutism that resolved after the therapy was discontinued (Achilli et al., 2016; Elraiyah et al., 2014; Hubayter & Simon, 2008; Lamont et al., 2018; Panzer & Guay, 2009). However, even these mild side effects of acne and hirsutism were not found to be significantly higher in the testosterone groups in some reviews (Panzer and Guay, 2009; Shifren & Davis, 2017). Other potential virilization effects such as voice deepening, androgenic alopecia, and clitoromegaly were not significant at physiologic level dosing (Achilli et al., 2016; Lamont et al., 2018; Shifren & Davis, 2017; Wierman et al., 2014). Some authors in their analyses also drew data from elevated testosterone states such as polycystic ovarian syndrome (PCOS), or supraphysiologic dosing for transgender men, to further comment on testosterone's safety (Al-Imari & Wolfman, 2012; Lamont et al., 2018; Wierman et al., 2014). Aside from the desired virilization with supraphysiologic dosing in transgender men, few adverse effects are seen; no increase in cardiovascular disease, breast cancer, cancer mortality or overall mortality has been seen, additionally women with PCOS do not have an increased risk of breast cancer (Al-Imari & Wolfman, 2012; Lamont et al., 2018; Wierman et al., 2014).

Breast cancer. In terms of potential long-term effects, many authors state that the most significant unknown risk is whether testosterone therapy might stimulate the development or growth of breast cancer via aromatization to estrogen (Al-Imari & Wolfman, 2012; Panzer & Guay, 2009; Shifren & Davis, 2017; Somboonporn et al., 2010). In the literature reviewed for this paper, there are varying degrees of commitment to conclusions about the safety of testosterone therapy relative to the risk of breast cancer. Some

conservative statements include: the data are conflicting; testosterone may confer a protective, neutral or increased risk effect; the risk remains unclear; and further study is required (Al-Imari & Wolfman, 2012; Hubayter & Simon, 2008; Shifren & Davis, 2017; Wierman et al., 2014). These equivocal statements stem from the lack of long-term studies, a plausible risk pathway via aromatization, the historic use of testosterone in the treatment of metastatic breast cancer because of testosterone's apparent antagonization of estrogen-stimulation in human breast tissue, and one study that showed a non-significant increase in breast cancer in the testosterone group (Lamont et al., 2018; Panzer and Guay, 2009; Shifren & Davis, 2017; Somboonporn et al., 2010). The highest quality safety data from RCTs is limited to studies shorter than 3 years, and data from the longest duration observational studies only spans 4 years. While those studies did not show an increased risk of breast cancer, they are relatively short considering that a woman could potentially want to use testosterone therapy for as long as she has an intimate partner (Al-Imari & Wolfman, 2012; Davis et al., 2016; Nachtigall et al., 2011). Other authors are less equivocal in their conclusions, and a number of authors conclude that despite limited data, there is no increased risk of breast cancer relative to the expected incident rates in similarly aged women (Al-Imari & Wolfman, 2012; Hubayter & Simon, 2008; Lamont et al., 2018; Nachtigall et al., 2011; Wierman et al., 2014). These evaluations have lead to a consensus that clinical evidence supports the short-term safety of testosterone therapy in the treatment of HSDD (Al-Imari & Wolfman, 2012; Davis et al., 2014; Shifren & Davis, 2017; Wierman et al., 2014). Unfortunately, women with sexual function concerns often require long-term treatment as they are prone to recurrence of symptoms after discontinuation of testosterone therapy (Wierman et al., 2014).

Informed Consent

The importance of fully informing a patient of the potential benefits and risks associated with testosterone therapy is emphasized in a number of the reviews and guidelines (Hubayter & Simon, 2008; Lamont et al., 2018; Shifren & Davis, 2017; Wierman et al., 2014). Hypothetical risks of testosterone therapy, known mild adverse effects demonstrated in clinical trials, and the potential risks associated with the off-label use of compounded rather than licensed preparations of testosterone all need to be thoroughly discussed with patients; and these discussions fully documented in the medical record (Hubayter & Simon, 2008; Shifren & Davis, 2017; Wierman et al., 2014).

Route of Administration

The route of administration of testosterone can affect efficacy, engender differing adverse effects, and influence the risk of unintentional supraphysiologic dosing (Somboonporn et al., 2010). Researchers have conducted clinical trials in order to evaluate most practicable routes of administration including oral, sublingual, buccal, intramuscular injection, subcutaneous injection, implantable pellets, transdermal patches, percutaneous creams, and percutaneous gels for efficacy and safety (Hubayter & Simon, 2008; Panzer & Guay, 2009; Shifren & Davis, 2017; Somboonporn et al., 2010). Despite producing a comprehensive list of trialled routes, the literature in this review did not specifically address the short comings or benefits of each available route, but the literature did yield useful information to evaluate.

Inherent issues with available routes. Sublingual/buccal administration was found to cause unstable serum profiles due to rapid absorption and turnover (Hubayter & Simon, 2008). Intramuscular injection, often causes supraphysiologic peaks followed by troughs

prior to the next injection as do implantable pellets, and both are characterised as inconvenient, potentially painful, with risk of infection, and any resultant supraphysiologic levels cannot be readily rectified (Hubayter & Simon, 2008; Shifren & Davis, 2017). Oral administration would perhaps be the most convenient route, but clinical trials demonstrate poor absorption of oral formulations (Shifren & Davis, 2017). Moreover, oral testosterone lowers high-density lipoprotein levels which may adversely increase cardiovascular risk, and oral formulations are also associated with toxic first-pass effects to the liver (Al-Imari & Wolfman, 2012; Shifren & Davis, 2017). Transdermal gels and emulsions are messy, absorption between individuals is erratic, and testosterone can be transferred to other women or children in close contact (Hubayter & Simon, 2008; Shifren & Davis, 2017). Transdermal patches largely avoid the mess, and the risk of inadvertent transfer of gels and emulsions, however, they are only available at concentrations suitable for male use. Although none of the routes is without problems, the consensus amongst the studies is that transdermal testosterone should be the clinical standard, and is the best way to reduce adverse events (Achilli et al., 2016; Lamont et al., 2018; Panzer & Guay, 2009; Shifren & Davis, 2017).

Transdermal testosterone. Transdermal testosterone patches have been studied in a number of trials, have been shown to be efficacious, and are able to maintain testosterone in the premenopausal physiologic range (Hubayter & Simon, 2008; Shifren & Davis, 2017). Despite this, the lack of long-term safety data resulted in the FDA declining to approve a transdermal patch for women (Shifren & Davis, 2017). However, in the European Union a 300 mcg/24 hr transdermal patch was approved for the treatment of HSDD in surgically menopausal women on concurrent estrogen therapy (European Medicines Agency, 2006; Panzer & Guay, 2009; Wierman et al., 2014). Without a suitable transdermal patch available

to women in Canada, ointments, gels, or creams are the only options to obtain the benefits of therapy, while capitalizing on the reduced risk of adverse effects inherent to the transdermal route. Some of the advantages of transdermal administration are that serum levels can be increased or decreased readily in response to bloodwork, there is no hepatotoxic first-pass effect on the liver, and there is no effect on serum lipids or high-density lipoproteins (Al-Imari & Wolfman, 2012; Panzer & Guay, 2009; Shifren & Davis, 2017).

Dose of Testosterone

Supraphysiologic doses of intramuscular testosterone that approached the lower limit of normal for men, produced a dramatic increase of 2.7 SSE per week in women who did not have sexual desire concerns (Shifren & Davis, 2017). However, the consensus in the literature is that physiologic dosing to high-normal premenopausal levels is preferred (Al-Imari & Wolfman, 2012; Davis et al., 2016; Hubayter & Simon, 2008; Lamont et al., 2018; Panzer & Guay, 2009; Shifren & Davis, 2017; Wierman et al., 2014).

Healthy premenopausal women synthesize about 300 micrograms (mcg) of testosterone daily, however, the exact dose of testosterone to treat women with HSDD is not known (Hubayter & Simon, 2008; Panzer & Guay, 2009). Elraiyah et al. (2014) concluded that, in 35 RCTs covering more than 5000 patients, testosterone dose, and levels achieved, were insufficient for meta-analysis. Conclusions from studies that utilized transdermal patches include that their may be a ceiling effect in women with HSDD, with dosages of 450 mcg daily conferring no additional benefit over 300 mcg daily (Hubayter & Simon, 2008). These 300 mcg per day patches were subsequently used in many trials, but these are not available in the North American market (Shifren & Davis, 2017). In studies that used transdermal gels, ointments, or creams there are a wide variety of doses reported in the

reviewed studies, ranging from 4 milligrams (mg) to 10 mg daily (Hubayter & Simon, 2008; Panzer & Guay, 2009). Authors referencing a 1% testosterone cream, approved for use by women in Australia, suggest an initial application of 0.5 grams per day (5 mg per day) as total and free testosterone can be influenced in a predictable dose dependent fashion with 1% testosterone cream (Hubayter & Simon, 2008; Panzer & Guay, 2009; Shifren & Davis, 2017).

There are no explanations in the reviewed literature for the widely variable dosing regimens, and given that in the described studies the targeted therapeutic level was the high-normal physiologic range for free testosterone, the widely variable doses are perhaps confusing (Al-Imari & Wolfman, 2012; Hubayter & Simon, 2008; Panzer & Guay, 2009; Wierman et al., 2014; Somboonporn et al., 2010). This will be further explored in the discussion section.

Monitoring testosterone levels. The monitoring of testosterone levels receives more discussion than the appropriate dose, in the papers. A number of the authors conclude that liquid chromatography/mass spectrometry should be used to measure total testosterone levels; free testosterone levels should be measured by equilibrium dialysis, ultrafiltration, or calculated using Sodergard equations that take into account SHBG and albumin levels; and that immunoassays are unreliable analyses that should be avoided (Davis et al., 2016; Lamont et al., 2018; Panzer & Guay, 2009; Wierman et al., 2014). In further conclusions about testosterone levels, authors express that an important consideration is the concurrent use of estrogen therapy, as oral estrogens increase SHBG levels (Hubayter & Simon, 2008; Wierman et al., 2014). Due to the high affinity of SHBG for testosterone, elevated levels of SHBG can increase the total testosterone level due to reduced clearance (Hubayter & Simon,

2008). However, supraphysiologic total testosterone levels may not reflect bioavailable or free testosterone levels, and corresponding androgen activity when SHBG levels are elevated (Hubayter & Simon, 2008; Davis et al., 2016). The androgenic state is thought to correlate better with free testosterone rather than total testosterone values, and several authors conclude that free testosterone should be followed and kept in the high-normal range for premenopausal women (Panzer & Guay, 2009; Davis et al., 2016; Shifren & Davis, 2017). Despite this recommendation, none of the papers describe what values constitute the normal range, except to say that they vary according to the assay and that the normal range has not been accurately established (Davis et al., 2016). In terms of a monitoring schedule, in order to safeguard against excessive use or serum androgen excess, it is suggested that testosterone parameters should be measured at baseline, 3 to 6 weeks after initiating therapy, after dose changes, and approximately every 6 months if on a stable regimen (Shifren & Davis, 2017; Wierman et al., 2014).

Continuation of Therapy After a Successful Trial

Although there are recommendations of when to end a trial of testosterone that has not shown benefit, there is little discussion of how long an effective therapy can be continued. Somboonporn et al. (2010) suggest limiting therapy to short-term use, because of the lack of long-term studies, but they do not define ‘short-term’ in their recommendation. Shifren and Davis (2017) and Wierman et al. (2014) suggest measuring hormone levels every 6 months, but provide no recommendation for how long this could continue. What is recognized by Wierman et al. (2014) is that symptoms of sexual dysfunction often recur after discontinuation of testosterone therapy and that sexual dysfunction requires long-term treatment.

Off-label Prescribing and Compounding

Not only does a clinician need to be aware of the potential safety concerns of the intended therapy, but also a clinician has to consider that there are no licensed preparations of testosterone for women. In the review of the literature, several authors identified the lack of an approved testosterone formulation for women in the North American market as a safety concern (Davis et al., 2016; Hubayter & Simon, 2008; Lamont et al., 2018; Shifren & Davis, 2017; Wierman et al., 2014). Currently, use of approved male formulations or compounded products are the only options in Canada, but authors suggest that ideally, they should not be used (Davis et al., 2016; Wierman et al., 2014). Due to the fact that compounded products are individually created by pharmacies, the efficacy or safety of any particular preparation can not be attested to (Hubayter & Simon, 2008; Wierman et al., 2014). Further, marketplace safety surveillance for compounded products seldom occurs, and is not comparable to the post-marketing surveillance of approved medications (Shifren & Davis, 2017).

Summary

In this findings chapter, data was extracted from eleven select pieces of literature in order to answer the question: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause? Analysis of the literature enabled identification of several key themes woven throughout the papers and these findings offer key information pivotal to answering the research question. Safety of testosterone therapy was widely addressed in the literature and the consensus in the findings is that with transdermal physiologic-level dosing, mild acne or unwanted hair growth would be the most likely adverse effects. Despite this, many trials did not report

these effects as occurring at higher levels in the treatment groups than in the comparison groups. More serious adverse effects like virilization, and breast cancer, were never statistically significant. However, further long-term safety studies were widely advocated.

Clinical trials have explored numerous routes for dosing, and transdermal administration has emerged as the clinical standard. This consensus is based on relative ease of administration, ability to maintain steady physiologic serum levels, ability to easily adjust doses in response to serum levels, and avoidance of undesirable first-pass liver effects. The literature highlights concern around monitoring serum levels, as there is good evidence that many laboratory tests are not suitable for accurately determining serum concentrations in the therapeutically intended normal female physiologic range. Further, reference ranges vary according to the analytic modality, and there is no clear consensus on what constitutes the normal range. Lastly, there is guidance around an appropriate timeframe for a trial, but little guidance around how a trial should be evaluated, or how long therapy might safely continue if the woman is deriving benefit.

The lack of a licensed testosterone product for women was also identified as a safety issue as it necessitates off-label or compounding prescription. Prescription of compounded medication provides relatively few guarantees of purity, or efficacy, and there is a lack of post-marketing surveillance. Off-label prescription was also seen as adding another important dimension to the required informed consent discussions addressing potential benefits, side effects, and unknown long-term risks.

In the next section, the themes presented above are further discussed along with implications for practice.

Chapter 5: Discussion and Implications for Practice

In the previous section, information relevant to the prescription, and evaluation of efficacy and safety, were identified in the literature and presented as findings. In this section of the integrative literature review these ideas are further discussed and synthesized to answer the clinical research question: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause? The intent is to provide NPs, and other primary care clinicians, with evidence-informed recommendations for the management of testosterone therapy in women with a diagnosed condition of low sexual desire.

Low Sexual Desire Diagnoses

As discussed in the introduction and background, there is controversy as to what diagnosis is most relevant to a problematic condition of low sexual desire. Even though the majority of the reviewed literature was published after the DSM-5 sexual dysfunction criteria were available in 2013, any mention of the new DSM-5 diagnosis compared to the DSM-IV diagnosis of HSDD was brief. Although the DSM provides a recognized classification system for female sexual dysfunction, it is not the only internationally recognized classification system (McCabe et al., 2016). Many sexual medicine practitioners continue to use the DSM-IV-TR diagnosis of HSDD, and others have advocated for a hybrid definition derived at the International Consultation on Sexual Medicine (ICSM) in 2016 (McCabe et al.). This ambiguity in the appropriate diagnostic criteria for a condition of low sexual desire can represent a diagnostic challenge in primary care. This is part of the art of primary care, where clinical judgement, by considering the available evidence, is needed to determine the best course of action in the face of ambiguity.

Clinicians can become versed in distilling the essence of a problem, and with fluency in the concept, it might not be critically important whether the diagnosis is exactly in line with HSDD or FSIAD, if it is evident that there is a condition of low sexual desire, and the woman experiencing this is significantly distressed. I suggest that clinicians already have a certain tolerance for using synonyms for disease classifications, and can be comfortable with the concept of defining the same clinical entity in different ways. As an example, in clinical practice in B.C. although a diagnosis might be made using strict DSM criteria, clinicians need to translate the DSM diagnosis into the vocabulary of the ICD-9 diagnostic codes for the Medical Services Plan. These ICD codes do not align well with the DSM classifications. To illustrate, a reference list of ICD-9 codes provided for use by the Medical Services Plan provides '302.7 frigidity' as the only moderately relevant, yet archaic, diagnosis, (Province of British Columbia, n.d.).

What may be more important is clinician awareness that there is controversy around the medicalization and diagnosis of mild or transient conditions, especially in the arena of sexual health. In general, labeling any aspect of sexuality as a dysfunction or disorder can be problematic, as colloquially there are connotations of judgment or inadequacy. If a practitioner elects to use a potentially stigmatic term such as sexual dysfunction or disorder, simply to mean a condition where a woman is unable to participate in her sexual relationship as she would want to, it might be valuable to discuss with the patient the intention behind the terminology used.

As noted in the background, DSM-5 introduced severity and duration criteria in part to raise the bar for diagnosis (Graham, 2016). Cognizance of making a carefully considered diagnosis, so not to inadvertently label women who do not actually have a sexual desire

disorder, might be more important than fastidiously using HSDD or FSIAD criteria. This might be reasonable considering the substantial overlap in numbers of women found to meet both the HSDD and FSIAD criteria, and the assertion that FSIAD may be thought of as a more severe subset of HSDD.

The duration criteria added to FSIAD may be an area where flexibility might be warranted. There is evidence that sexual dysfunctions that remain untreated can worsen, as a dysfunctional pattern is reinforced over time (Nappi et al., 2016). This is particularly true for dyspareunia and is postulated to be similar in conditions of low sexual desire (Nappi et al., 2016). If as a consequence of low sexual desire, dysfunctional patterns develop and become ingrained in the relationship, the entrenchment may compound the issue and make it more challenging to restore desire (McCabe et al., 2016). FSIAD requires symptom criteria to be present for six months prior to diagnosis, whereas the DSM-IV-TR did not specify duration, and the ICSM suggest a three-month duration. However, ascertaining the level of distress and the holistic impact of the clinical issue, as well as inquiring about the patient's priorities, might justify flexibility in the stringent application of the time criterion, and making a diagnosis of a condition of low sexual desire. This would need to be balanced with being mindful that labeling, overdiagnosis, and unwarranted prescription should be avoided (Tiefer, 2010).

Deciding on Testosterone Therapy

Treatment of a diagnosed condition of low sexual desire is not straight forward, and not as simple as simply prescribing testosterone. The complex background of biopsychosocial factors that influence sexual desire as well as patient preferences make it challenging to determine the best course of therapeutic intervention. In conditions of low

sexual desire, low testosterone levels are likely contributory to, rather than the sole cause of, the issue (Feldhaus-Dahir, 2009). The consensus in the literature, as presented in the findings, is that testosterone therapy is appropriate for use when other contributions to low sexual desire have been ruled out. The most straightforward clinical scenario might be when a woman who previously had personally satisfactory levels of sexual desire, then presents with, or screens positive for, low sexual desire after undergoing an oophorectomy. This would contrast markedly from a scenario of evaluating and treating a woman who has always had low levels of sexual desire.

If after having undergone an oophorectomy, a woman meets criteria for the diagnosis of a condition of low sexual desire and reports that the quality of her intimate partner relationship is good, and she does not report fatigue, stress, or lack of time, it may be clinically appropriate to initiate testosterone therapy. However, even in a presentation that is more convincing of low androgen levels being contributory, a clinician should still consider potential involvement of culturally informed beliefs about menopause. Surgical menopause, with its accompanying loss of fertility, can affect a woman's attitudes regarding sexuality, as well as her self-perception of femininity and sexual desirability (Shifren and Davis, 2017).

No threshold testosterone level has been identified below which sexual dysfunction consistently exists, and therefore measurement does not aid diagnosis (Davis et al., 2016). However, preliminary measurement of total testosterone and free testosterone will serve to ensure that testosterone levels are not unexpectedly elevated, as well as provide a baseline comparison for levels achieved with testosterone therapy (Wierman et al., 2014). Evaluation of adequate estrogen therapy is also important in order to determine if desire is being impacted by changes such as vulvovaginal atrophy, vasomotor symptoms, or trouble

sleeping (Shifren & Davis, 2017). Discerning whether the condition of low sexual desire pre-existed the oophorectomy would be important, as this might suggest that other psychosocial aspects may be contributory rather than sex steroid levels.

For a woman who had diminished desire prior to an oophorectomy, or a woman that has had an oophorectomy but the psychosocial circumstances in her life or relationship have changed after the surgery, the literature suggests that non-pharmacologic therapy such as sex therapy or brief intervention techniques should be trialled first (Lamont et al., 2018). Perhaps this would be reasonable even in women where the suspicion of low testosterone is higher. The effect size of testosterone therapy has been judged to be similar in character to psychotherapy (Pyke & Clayton, 2018). However, non-pharmacologic solutions may be more desirable from the view point of risk mitigation, and I suggest they may empower the patient through fostering the development of self-management strategies (Pulvirenti, McMillan, & Lawn, 2012; Shifren & Davis, 2018).

Although I have not found published clinical trials directly comparing the efficacy of testosterone treatment versus the efficacy of non-pharmacologic therapy, the comparison of other pharmaceuticals to non-pharmacy is a focus of some study. A current study is being conducted to ascertain whether premenopausal responders to flibanserin, which has been demonstrated to provide similar moderate increases in sexual desire, derive further benefit with the addition of sex therapy sessions (U.S. National Library of Medicine, 2018). When that data is published it may be informative to see if there is evidence of a synergistic effect between medical therapy and sex therapy in addressing sexual health concerns. I suggest that a demonstrated additive effect realized by combining psychosocial interventions with

pharmacy would serve to support the assertions of Berry and Berry (2013) of the value of integrative biopsychosocially informed care in sexual health.

Professional Responsibility of Informed Consent

In order to make a clinical decision in partnership with a woman to initiate testosterone therapy, informed consent is imperative. This not only comes from the literature but also from the Scope of Practice guidelines for NPs in B.C., and thus is a practice expectation. Specifically, clients need to be informed of: 1) expected action of the drug; 2) duration of therapy; 3) specific precautions or instructions; 4) potential side effects or adverse effects and actions to take should they occur; 5) potential interactions with foods, drugs, or other substances; and 6) recommended follow up (BCCNP, 2018a). NPs must also use current evidence to support prescription decisions and have the competence to monitor and manage a client's response to a drug (BCCNP, 2018a). The assembled literature also advocates that considerations surrounding off-label prescribing, requisite in testosterone therapy for women in Canada, need to be addressed and the conversation documented in the patient's medical record (Lamont et al., 2018; Wierman et al., 2014).

Below are key discussion points derived from the reviewed literature that should aide NPs in addressing information that should be shared with the client.

Expected action of the drug. The mechanism of action of testosterone is unknown but it is thought to act both peripherally, and centrally in the brain, where it might modulate excitatory and inhibitory processes via testosterone receptors or estrogen receptors after aromatization (Bancroft et al., 2009). The therapeutic effect of increased sexual desire is typically moderate, not dramatic, and may take six to eight weeks to occur (Shifren & Davis, 2017).

Duration of therapy. Initially the therapy should be conducted as a trial to see if the patient derives benefit (Lamont et al., 2018; Shifren & Davis, 2017). Responders typically see the most benefit within the first three months, and if by six months there is no meaningful benefit, the trial should end (Davis et al., 2016). It is unclear from the literature how long successful therapy can safely continue. Ongoing assessment for efficacy, adverse affects, and acceptability of the therapeutic regimen, as well as review of newly published literature may inform this. Due to the lack of guidance in the reviewed literature, consultation with a specialist might be reasonable for prolonged therapy. Further, current literature on responsible prescribing supports the practice of deprescribing when warranted (Bruyère Research Institute, 2019). Even if a therapy has historically been effective, a discontinuation trial may be a clinical consideration to assess if ongoing therapy is necessary. (Bruyère Research Institute, 2019).

Specific instructions, potential adverse effects and actions to take. Literature suggests that application sites should be rotated so to reduce the likelihood of local hair growth (Lawley Pharmaceuticals, 2016; Shifren & Davis, 2017). To further mitigate the risk, the lateral thigh or buttocks are recommended sites (Shifren & Davis, 2017). Use of these sites also reduces the likelihood of unintentional skin-to-skin transfer, compared to application to the upper torso or arms (Shifren & Davis, 2017). Additionally, avoiding application to the arms reduces breast exposure through lymphatic drainage (Shifren & Davis, 2017). Women should wash their hands with soap and water after application and guard against inadvertent transfer to other women or children; transfer to men is not a concern as they have a much higher endogenous level of testosterone (Lawley Pharmaceuticals, 2016; Shifren & Davis, 2017).

Patients should be informed that the only statistically significant adverse effects seen were mild increased hair growth and mild acne, and other virilization effects were not seen. (Shifren & Davis, 2017). More serious risks such as an increased risk of breast cancer are not thought to occur, but long-term studies are lacking. In the event of unwanted hair growth or acne, the patient should return to care for evaluation, which should include assessment of serum testosterone levels. If necessary, the dose can be tapered or testosterone discontinued. Testosterone levels would be expected to fall to baseline within 2 to 5 days and adverse effects should resolve (Lawley Pharmaceuticals, 2016; Shifren & Davis, 2017).

Lawley Pharmaceuticals (2014, 2016) provide consumer and practitioner-oriented product information for their 1% testosterone cream, which is licensed for use by women in Australia. These publications could be useful in patient counselling as they specifically address use of transdermal testosterone cream by women; whereas testosterone drug monographs in North America are only written relative to male use of testosterone.

Potential interactions with foods, drugs, or other substances. Any medication that might affect the levels of SHBG could change the serum level of free testosterone available for bioactivity. Perhaps the most relevant medication for women after oophorectomy is concomitant estrogen therapy, as oral estrogen preparations increase SHBG concentrations (Wierman et al., 2014). Women should be advised that any change in oral estrogen dose or formulation may influence SHBG levels, and additional bloodwork would be required to ensure that serum testosterone measures remain in the target range. Other medications known to affect SHBG levels include medications that affect the hypothalamic pituitary gonadal axis, including glucocorticoids, anti-epileptics, aromatase inhibitors, thyroid

hormone and anti-thyroid agents (Gyawali et al., 2018). Adding, removing, or titrating these other medications would require increased monitoring of SHBG and free testosterone.

Recommended follow up. Ongoing follow up is required for women prescribed testosterone therapy. Evaluation of efficacy, and assessment for adverse effects, should be conducted at follow up appointments. As shown in the findings, literature suggests that total testosterone, free testosterone, and SHBG should be drawn at baseline, three weeks after initiation of therapy, after dose changes, or use of a new supply of compounded medication. When stable levels are achieved it is recommended that bloodwork should still be checked every six months for safety (Wierman et al., 2014). Since reference ranges are known to vary by assay, use of the same lab service would be beneficial. Based on the evidence from the literature, I suggest ordering baseline bloodwork, bloodwork after three weeks followed by dose adjustments if needed, bloodwork in another 3 weeks, and then a clinical appointment for evaluation of efficacy and adverse effects at around 7 weeks after initiating therapy (Shifren & Davis, 2017).

Evaluating Efficacy

Although in clinical trials, quantitative data was collected in order to be able to demonstrate statistical significance, it is unclear what approach should be used in primary care. SSE counts, which have long been the primary endpoint in sexual desire clinical trials, have been criticized as an indirect measure of sexual desire (Kingsberg & Althof, 2011). As illustrated in the circular sexual response model by Basson (see Figure 2), there are numerous reasons that a woman may engage in sexual activity other than her own sexual desire. Although SSE likely has some relevance, literature suggests that it should be

relegated to a secondary endpoint in trials, and subjective patient reported outcomes may be a better way to determine therapeutic efficacy (Pyke & Clayton, 2018).

Rating scales can be incorporated into primary care practice in order to quantitatively evaluate changes and thus infer efficacy. Indeed, some primary care providers and clients may prefer this methodology and choose to utilize it, much as clinicians might use the Patient Health Questionnaire (PHQ-9) to determine degree of response to interventions in depression therapy. Clinical researchers have developed and used numerous rating scales to evaluate improvement of HSDD, but as yet there are no analogous scales for FSIAD (Meston & Stanton, 2017). A clinician can choose among many available scales. The Female Sexual Function Index - desire subscale (FSFI-d), developed in 2000, is easy to use as it only consists of two questions, but it lacks information about sexual behaviour and attitudes towards partners (Pyke & Clayton, 2018). The Female Sexual Distress Scale – Revised (FSDS-R) facilitates quantification of sexual distress, and can be used to assess therapeutic response in patients with HSDD (DeRogatis, Clayton, Lewis-D'Angostino, Wunderlich, & Fu, 2008). The Profile of Female Sexual Function, was specifically developed for the assessment of HSDD in women that underwent oophorectomy, and can be used in assessing therapeutic change (McHorney et al., 2004). Which scale is best is not a settled answer and is a current discussion point in the literature. Pyke and Clayton (2018) reviewed 12 validated HSDD scales and recommend that the 9-item Elements of Desire Questionnaire (EDQ), as well as a measure of sexual frequency might best demonstrate the clinical relevance of a treatment. Yet, despite the availability of numerous scales developed for clinical trial use, it is unclear whether quantitative measurement is necessary in primary care; as literature supports the idea that women are able to assess their own benefit of

treatment and are able to identify themselves as responders or non-responders (European Medicines Agency, 2006).

It is potentially problematic that the tools discussed in the literature are only validated for use with the diagnosis of HSDD, and that there are no tools validated for FSIAD (Meston & Stanton, 2017). Even Pyke and Clayton's review article published in 2018, five years after the introduction of FSIAD, is HSDD centric. For clinicians that aim to adhere to the FSIAD diagnostic criteria, and evaluate treatment efficacy in relation to the FSIAD diagnosis, trusting a woman's intrinsic capacity to appraise the value of the treatment might be a reasonable approach. It is arguable that given the nature of sexual desire, qualitative information might be better than quantitative (Pyke & Clayton, 2018). No matter the decision, certainly a composite evaluation of SSE, decreased distress, and increased desire, as well as the acceptability of the therapeutic modality including the requisite bloodwork, and ongoing clinical follow-up, would be appropriate.

Prescription of Testosterone

Route. When it comes to prescription, some authors contend that testosterone may improve symptoms of sexual dysfunction regardless of route (Jayasena et al., 2019). The pros and cons of many of the available routes were presented in the reviewed literature and appear in the findings section, however, intravaginal testosterone was not discussed in the reviewed literature. Intravaginal testosterone has been investigated in the treatment of vulvovaginal atrophy which can be accompanied by sexual dysfunction including decreased sexual desire (Bell, Rizvi, Islam, & Davis, 2018). Sexual desire was seen to improve, but it is unclear if this was due to sex steroid support of the local tissues, and a systematic review concludes that higher quality evidence, than what is currently published, is needed to

establish efficacy and safety of intravaginal testosterone (Bell et al., 2018; Jayasena et al., 2019). Several clinical trials have evaluated a transdermal matrix patch, and many others have investigated transdermal creams and gels. Consensus in the reviewed literature is that, transdermal testosterone is the recommended route of administration (Achilli et al., 2016; Lamont et al., 2018; Panzer & Guay, 2009; Shifren & Davis, 2017). However, transdermal patches are only commercially available at concentrations suitable for male use, and these patches should not be cut in an attempt to deliver an appropriate dose for women (Basson, 2010). With the absence of licensed products for women in North America, the clinical norm is to prescribe compounded products off label (Nappi, 2015).

Dose and adjustment. Perplexing is the variety of transdermal doses that have been used in clinical trials that have ostensibly sought to achieve and maintain physiologic levels of free testosterone. For example, the Intrinsa transdermal patches studied and eventually licensed in the European Union delivered 300 micrograms per day, whereas the dose of transdermal testosterone cream licensed for use in women in Australia, AndroFeme 1% is 5 milligrams per day, which is 5000 micrograms per day (European Medicines Agency, 2006; Lawley Pharmaceuticals, 2016). This discrepancy is apparently due to the different pharmacokinetics between a transdermal patch and transdermal cream. Additionally, patches are prescribed per the dose that they deliver through the skin (i.e. 300 mcg/day); whereas gels and creams are prescribed by the total amount of product applied (i.e. 5 mg/day), with no indication how much will be absorbed (Pastore, Kalia, Horstmann, & Roberts, 2015). Further, systemic bioavailability of a transdermal cream is only about 10%, and patches are far more efficient at delivering medication (Pastore et al., 2015). Although the outermost layer of the epidermis, the stratum corneum, is only 10-15 cells thick, it is an extremely

effective barrier to the absorption of foreign compounds (Marjukka-Suhonen, Bouwstra & Urtti, 1999). The Intrinsa matrix patch had an occlusive polyester protective film that prevents transfer to clothing, ensured full hydration of the stratum corneum, and the matrix layer also contained sorbitan oleate as a penetration enhancer (European Medicines Agency, 2006; Pastore et al., 2015). Penetration enhancers can increase absorption several fold (Marjukka-Suhonen et al., 1999).

In terms of prescribing testosterone to women, the literature comments that licensed male products are inappropriate due to the risk of supratherapeutic dosing, as the patches, metered pump doses, or individually packaged doses are too potent; yet there is also criticism of custom compounded formulations (Davis & Worsley, 2014). Based on the evidence, one of the safest ways to prescribe a testosterone cream to women in Canada would be to prescribe a 1% cream that has been licensed for use in hypogonadal males, via a device that can accurately dispense the required amount of cream. Accurate delivery of a prescribed amount of a commercially manufactured cream, would help address supratherapeutic dosing concerns, and can be accomplished using graduated syringes or fillable metered-dose devices available to pharmacies such as Topi-CLICK®. Further, use of a commercially manufactured and licensed 1% formulation, even though it is for men, would avoid many of the issues with compounded products identified in the literature such as product instability, inconsistent purity, variable concentration, and erratic bioavailability (Gudeman, Jozwiakowski, Chollet, & Randell, 2013; Grober et al., 2015; Kawano & Ho, 2012). In general, for safe prescribing, it is recommended to use an available FDA approved product rather than a compounded product (Gudeman et al., 2013; Sellers & Utian, 2012). Currently however, pharmacies often custom compound testosterone cream to different

concentrations when dose adjustment is required (W. Bedford, personal communication, December 11, 2018). This allows a patient to receive varying amounts of testosterone while always applying the same amount of cream. Further, the standard of practice for compounded creams is to specify a beyond-use-date of 30 days after compounding, meaning that any compounded cream should not be used after this 30-day timespan (Allen, 2011). However, frequent compounding of new batches of testosterone cream is problematic, as research highlights inconsistency in testosterone concentrations amongst compounded products, within-batch, between-batches, and between pharmacies (Grober et al., 2015). If electing to use a compounded product, concerns with product consistency could possibly be best minimized if the patient reliably uses the same compounding pharmacy, as this should eliminate more variables that can influence product consistency. Yet, even with this approach, overarching concerns about the quality of compounded preparations remain unresolved.

Unlike many medications that are prescribed at set doses, testosterone therapy needs to be specifically tailored to the individual. Using literature that details the use of a transdermal cream, an appropriate starting dose of testosterone cream would be 5 mg daily applied to the lower torso and outer thigh (Fooladi, Reuter, Bell, Robinson, & Davis, 2015; Lawley Pharmaceuticals, 2016). The dose needs to be adjusted in response to periodic bloodwork, however, the literature does not detail a protocol for titration. That said, studies have shown that total and free testosterone rise in proportion to the administered dose, however, it is not a simple linear relationship (Fooladi et al., 2015; Singh et al., 2006). For example, in a trial evaluating 1% testosterone cream, it was found that doubling the dose from 5 mg daily, only resulted in a 30% increase in total testosterone, and a 31% increase in

free testosterone (Fooladi et al., 2015). Other studies have shown that serum levels begin to decline between 24 and 36 hours after transdermal administration and are expected to fall to baseline within 2 to 5 days (Lawley Pharmaceuticals, 2016; Shifren & Davis, 2017; Singh et al., 2006). Without a licenced product that comes with an established protocol, it is apparent that titration of testosterone therapy requires clinical judgement.

Testosterone monitoring. The evidence establishes that free testosterone is the appropriate parameter to measure and titrate, as this parameter is not influenced by variations in SHBG which can significantly impact the amount of total testosterone that is bioavailable. However, in B.C. the available tests are total testosterone and calculated bioavailable testosterone (cBAT) (Guidelines and Protocols Advisory Committee [GPAC], 2018). Additionally, in B.C. all bioavailable and free testosterone values are calculated rather than directly measured (GPAC, 2018). Regardless of direct measure or calculation, bioavailable testosterone and free testosterone are not the same, as bioavailable testosterone includes both free testosterone, and the fraction of testosterone that is lightly bound to albumin. Yet, calculated free testosterone and cBAT are functionally and diagnostically equivalent due to the excellent correlation between free testosterone and bioavailable testosterone (GPAC, 2018; Vermeulen, Verdonck & Kaufman, 1999). Despite this, a clinician needs to be aware whether laboratories are reporting cBAT or calculated free testosterone, as cBAT levels are around 20 times higher than free testosterone levels (Vermeulen et al., 1999). In practice, either value can be used to monitor and titrate testosterone therapy so long as the clinician consistently uses the correct reference range (GPAC, 2018; Vermeulen et al., 1999).

In B.C., NPs are authorized as referring practitioners in the Laboratory Services Act (Province of British Columbia, 2015). As such, NPs can order any fee-for-service laboratory service listed in the Laboratory Services Payment Schedule that is within their scope of practice, as long as any GPAC clinical practice guidelines are specifically considered (Province of British Columbia, 2015). A 2018 B.C. Guideline on testosterone testing concludes that testosterone testing is not useful for investigating low libido in women, but is useful if overuse is suspected or if there is unexpected virilization during testosterone therapy (GPAC, 2018).

Medical Service Plan (MSP) coverage of associated lab fees for testing testosterone in women is unclear, and this may be an important financial consideration for some women. The B.C. Laboratory Services Payment Schedule is descriptive of testosterone testing for men, leaving uncertainty in the coverage of testosterone monitoring in women (Province of British Columbia, 2019). I received contradictory information regarding MSP coverage when inquiring over the phone at Valley Medical Laboratories in Kelowna B.C., and LifeLabs in Kamloops B.C. In discussion with a consultant pathologist, who is the clinical director for chemistry analysis for LifeLabs in B.C., it was explained that MSP is only likely to cover testosterone testing where women have abnormal elevations of testosterone, as there is no accepted standard for a deficient state (W. Schreiber, personal communication, February 12, 2019).

As described in the literature, reference ranges vary according to the assay and therefore are independently determined and provided to clinicians by the laboratory. Where multiple laboratory services exist, patients should be encouraged to use the same laboratory as results from different laboratories may not be comparable (GPAC, 2018).

To provide some approximate numbers, the reference range for total testosterone levels in women is 0.52-2.4 nmol/L; and the reference range for free testosterone is 3.5-29.5 pmol/L (Province of British Columbia, 2017). Literature suggests that serum levels respond well to dose adjustment, and the upper level of the reference range for free testosterone is the therapeutic target. However, it is thought that the potential risks of testosterone therapy increase with dose, and there does not seem to be a tight correlation between serum testosterone levels and sexual function (Davis et al., 2016). Therefore, the evidence supports that titration to the top of the therapeutic target-range is not necessary if the woman is satisfied with her response at lower serum levels of free testosterone.

There can be circumstances with elevated SHBG where total testosterone can increase beyond the physiologic range, yet free testosterone remains near the therapeutic target or even low (Hubayter & Simon, 2008). Authors in the surveyed literature did not comment on how to contend with this scenario. However, the portion of the total testosterone that is bound to SHBG is in essence unavailable for binding to androgen receptors; as such the evidence suggests that a small elevation of total testosterone due to elevated SHBG is likely not clinically significant (Braunstein, 2007). However, if looking to further increase free testosterone levels, in the context of a small supratherapeutic elevation of total testosterone, a clinician may want to look at addressing factors that elevate SHBG rather than further increasing the dose of testosterone. Although SHBG levels can be affected by a number of variables, oral estrogen therapy is usually particularly relevant among women with bilateral oophorectomy as it is the standard of care (Siyam et al., 2018). Oral conjugated equine estrogen (CEE) therapy can double SHBG levels (European Medicines Agency, 2006; Hubayter & Simon, 2008). A clinician might consider changing

the estrogen from a CEE preparation to a non-CEE estrogen as these have a lessor effect on SHBG, or to transdermal estrogen as it does not increase SHBG (European Medicines Agency, 2006; Hubayter & Simon, 2008).

Duration of Therapy and Risk

There is guidance in the literature for the duration of a testosterone trial; efficacy might not emerge for 6-8 weeks, peaks and plateaus after 3 months of therapy, and therapeutic trials should end after 6 months if a woman is experiencing no benefit (Davis et al., 2016; Shifren & Davis, 2017; Wierman et al., 2014). However, there is little guidance for how long successful treatment can be continued. Braunstein (2007) suggests that physiologic doses are safe for up to several years, however, most literature suggests unquantified "short-term therapy". Since sexual desire issues are often persistent, this can present a clinical conundrum (Wierman et al., 2014).

From the literature it appears that the incidence of hirsutism and acne, the most common adverse effects, do not tend to increase with longer therapy, but instead corelate with elevated levels of serum testosterone (Nachtigall et al., 2011). Due to limited clinical data, it remains unknown whether there is any increased risk of breast cancer, or other adverse effects, with longer-term testosterone therapy (Nachtigall et al., 2011). Although an increased risk of breast cancer has not been demonstrated, even in clinical trials up to 3 to 4 years in duration, the consensus in the literature remains that there is not enough evidence to rule out an increased risk (Al-Imari & Wolfman, 2012; Jayasena et al, 2019). Since cancer is often associated with long term exposure to cancer promoting compounds, if testosterone somehow promotes breast cancer, perhaps through aromatization to estrogen, then long-term testosterone therapy would imbue elevated risk.

As a further discussion point on breast cancer risk, all women should be counselled to be familiar with their own breasts, and to be vigilant and seek care with any breast changes (Canadian Task Force on Preventative Health Care, 2018). Although women on hormone replacement therapy (HRT) tend to have mammography screening more frequently than women not on HRT, practice recommendations do not support this increased frequency (Chlebowski & Anderson, 2012; Kerlikowske et al., 2013). Testosterone therapy has not been shown to be associated with an increased risk of breast cancer, studies have shown that serum estrogen levels do not tend to rise with testosterone therapy, and testosterone itself has been shown to be breast protective in some studies (Goldstat, Briganti, Tran, Wolfe, & Davis, 2003; Nathorst-Böös, Flöter, Jarkander-Rolff, Carlström, & Schoultz, 2006). Evidence suggests that testosterone therapy does not warrant increased frequency of mammogram screenings.

Discussion of the unknown long-term risks with a woman requesting ongoing therapy would be critical to ensuring informed consent. A fully informed woman, further guided by her own values and tolerance for risk, may desire to continue testosterone treatment. The available literature does not indicate this would be an unacceptable decision if paired with ongoing evaluation of serum levels and surveillance for adverse effects. However, a more conservative approach of tapering the dose over time, or conducting periodic discontinuation trials might be more reasonable than indefinite therapy. As discussed in the background, women tend to be less distressed about low levels of sexual desire as they age (Dennerstein et al., 2006). It may be that even if sexual desire declines during a discontinuation trial, that the woman would be accepting of this; and not having to

worry about daily application of cream, recurrent bloodwork, and clinic visits, might align more with her contemporaneous values.

Stopping a Trial or Long-term Testosterone Therapy

There was no information in the selected literature suggesting how testosterone treatment should be stopped if there is no efficacy by six months, the patient has experienced adverse affects, or simply desires to stop therapy. A clinical decision would need to be made whether to abruptly discontinue or to taper the doses. Guidance in this decision might be inferred from how cross-over clinical trials were conducted. In a number of trials there were abrupt switches from active treatment to placebo, with no reported ill effects (Barton et al., 2007; El-Hage Eden, & Zoa Manga, 2007; Nathorst-Böös et al., 2006). There is not likely to be any definitive trial data to answer this question, considering cessation of HRT has been more widely studied, and there is still no consensus reached whether to taper or abruptly stop HRT (Crawford, 2015). I suggest that it would be clinically reasonable to try either approach, but a taper would be fairly easy to conduct and hypothetically might be an easier transition.

Summary

Whittemore and Knafl's (2005) methodology for integrative literature reviews was used in this capstone project in order to answer the question: How can nurse practitioners manage testosterone therapy to benefit women distressed by a diminished level of sexual desire after surgical menopause? Professional responsibilities around prescription and management of patients as detailed in the BCCNP Scope of Practice were also used as a guide for this work. Appendix 2 provides a tabulated summary of the evidence-informed recommendations.

Testosterone therapy has been shown to improve sexual desire and reduce sexually related distress, both key requirements for diagnosis of a condition of low sexual desire. Meta-analyses and guidelines support the use of transdermal testosterone in women who have entered surgical menopause and have subsequently been diagnosed with a condition of low sexual desire. Given the myriad biopsychosocial factors that influence sexual desire, a careful assessment is required to rule out factors other than low testosterone, that might be contributory, prior to prescribing testosterone. Complicating matters, there is ambiguity as to which diagnostic criteria should be applied, HSDD or FSIAD, and this is only likely to be resolved through clarifying concepts through research.

If testosterone therapy is prescribed, transdermal cream is the best option as it is easy to use, associated with fewer adverse effects, and can be titrated in response to periodic bloodwork to achieve and maintain free testosterone levels in the young premenopausal adult range. A 5 mg daily dose of a compounded or off-label testosterone cream is an appropriate starting dose. The use of compounded or off-label testosterone requires specific discussion with the patient and documentation to this effect in the medical record.

Literature supports that women can subjectively determine whether or not the testosterone is working for them, but there are rating scales available for desire and distress that clinicians may want to employ (Pyke & Clayton, 2018). However, these scales are only validated for HSDD. Patients should be informed that testosterone therapy is moderately effective for increasing desire, but if there is no meaningful response by three months, they are unlikely to derive benefit, and an ineffective trial should end by six months.

The most likely adverse effects, although still uncommon, are hirsutism and acne. More serious side effects like breast cancer have not been statistically significant in trials up

to four years in length, but long-term safety remains unknown. Successful therapy can reasonably continue beyond a short-term trial, with adequate monitoring, so long as the patient is adequately informed, and she is comfortable with the ambiguity of risk. However, periodic discontinuation trials might be a reasonable clinical option to determine if both low sexual desire, and associated distress persist.

Strengths and Limitations

A strength of this review is that there were many pieces of literature from which to choose in order to answer my research question. Consequently, I was able to select pieces of literature that constitute high quality evidence such as systematic reviews and meta-analyses, a Cochrane review, and guidelines based on such literature (Centre for Evidence-Based Medicine, n.d.). Use of this stratum of literature from the evidence-based medicine pyramid allows for confidence in the findings, which directly impacts the level of confidence in the recommendations. However, not all findings and recommendations derive from this higher level of evidence. While findings relative to safety, transdermal administration, and bloodwork monitoring parameters were distilled from higher level literature, some other findings and corresponding recommendations do not have as extensive support and represent my best effort at synthesizing the available evidence. These lesser supported recommendations include off-label use strategies, initial dosing, product application, determination of efficacy, and continuance or termination of therapy.

Perhaps one of the greatest limitations of this work is that this project constitutes my first effort as an integrative literature reviewer. Although I utilized the methodology described by Whittemore and Knafl (2005), a more experienced author may have distilled the body of literature to arrive at a different assemblage, which would invariably affect

findings and recommendations. Further, my inexperience as a clinician also presents a limitation. A more experienced clinician would likely have begun the inquiry from a more informed position; and their experience might facilitate deeper contextual analysis and further honing of recommendations. Nevertheless, this integrative literature review does provide an overview of the subject matter and practice recommendations that I believe are supported by quality published literature. Appendix 2 provides a tabulated summary of the evidence-informed recommendations.

Recommendations for Research & Education

Safety. It is evident in the literature that there is not enough long-term data on the safety of testosterone therapy in women. Therefore, to conclusively state that there are no increased serious health risks associated with testosterone therapy, is not possible. In fact, as mentioned previously, it was for want of long-term safety data, that the FDA declined to authorize Procter & Gamble's Intrinsa testosterone patch, despite agreeing that studies demonstrated efficacy (Basaria and Dobs, 2006). To date, there have still been no long-term safety trials, therefore, this remains an area where more research should be conducted. Satisfactory safety data from such trials could facilitate the approval and licensure of a testosterone product for women, thereby addressing some concerns associated with off-label and compound prescription practices. In addition to providing better safety data, long-term trials might also provide valuable information about appropriate duration of therapy, as this is not available in the current literature.

Conceptual clarity. Controversy in the diagnosis, and even the selection of a universally agreed to term for a condition of low sexual desire, might also benefit from more research. The latest iteration of the DSM provided the FSIAD diagnosis; yet this concept has

been criticized as being ideological rather than a concept studied and derived from clinical research (Davis et al., 2016). Balon and Clayton (2014) deride a lack of scientific evidence for the FSIAD diagnosis. It is evident that concerns around the terminology and criteria are not settled. In fact, although more than half of the 11 articles selected in this literature review were published after the DSM change from HSDD to FSIAD, only two papers briefly mention the current DSM-5 diagnosis. Validating the concept of FSIAD through clinical research could prove valuable in eliminating competing or outdated hypotheses. Establishing pan-professional concepts would add clarity to the field of clinical research and treatment.

Newer agents. Newer pharmaceutical agents such as flibanserin, approved for treatment of HSDD in premenopausal women, might also be evaluated for efficacy in women who have experienced surgical menopause and also have distressing low sexual desire. Women could benefit from comparative randomized controlled trials that ascertain which agent provides better efficacy and has a better safety profile. Certainly, an oral agent such as flibanserin, which requires no bloodwork monitoring or dose adjustment, may be more acceptable to women if it is equally effective and safe (Sprout Pharmaceuticals, 2018). Sexuopharmaceutical research is ongoing, and other upcoming products should be similarly evaluated to see if they might provide benefit to surgically menopausal women distressed by low sexual desire.

Synergistic approaches. The biopsychosocial model of treatment of sexual dysfunction advocates that all three domains should be addressed in treatment. In the review of literature for this paper, there was little literature evaluating the relative benefits of counselling versus medication, or a combination approach. Conducting research to

determine if enhanced benefits might be realized through concurrent non-pharma and pharmaceutical interventions may prove to be beneficial. Research would hopefully facilitate identification of synergic therapeutic approaches that increase sexual desire and decrease sexual distress.

Knowledge enhancement. Findings from the research proposed above could be used to improve the knowledge of primary care clinicians in the treatment of conditions of low sexual desire. However, research literature asserts that there is still much work to be done in the foundational didactic and clinical sexual health care education of primary care clinicians. Appropriate knowledge, skills, and attitudes regarding assessment and treatment of sexual health concerns will facilitate better care (Shindel et al., 2016). Although expertise in sexual health medicine will still likely require self-directed learning, a stronger educational foundation would be beneficial. This may continue to be challenging, as medical and NP programs are required to prioritize content for the limited number of contact hours available to educators. Educational emphasis on the value of holistic assessment, and the importance of broaching the topic of sexual health, may serve to initiate provider-patient conversations where historically no conversation would occur. Simple conversation guided by holistic principles may be the catalyst that allows discovery of sexual health concerns and exploration of patient centered solutions.

Conclusion

Following surgical menopause, a number of women experience a decline in their level of sexual desire which can cause sexual distress. Despite lack of definitive serologic evidence, this decline in libido has been attributed to lower levels of endogenous

testosterone due to the elimination of the ovarian contribution. This low testosterone hypothesis is supported by clinical research findings of improved sexual desire with therapeutic use of exogenous testosterone. As such there is guideline support for trialling testosterone therapy in women in this context. However, despite guideline support, there are no approved testosterone formulations for women, ostensibly due to the lack of long-term safety data. Consequently, clinicians interested in prescribing testosterone therapy are required to determine for themselves the safety considerations and how best to prescribe, monitor, and evaluate therapy. This integrative literature review provides context, analysis, discussion, and recommendations that can aid nurse practitioners in the primary care use of testosterone to benefit women experiencing distress due to reduced sexual desire.

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Appendix 1

Search Terms and Database Results

Database	Search Terms	Results
Medline Ebsco Filters: 2000-2018 English language	"sexual dysfunction, physiological+" OR "sexual dysfunction psychological+"; AND "female"; AND "testosterone+"; AND "drug therapy+"	103
CINAHL Filters: 2000-2018 English language	"sexual dysfunction, female+"; AND "testosterone+" OR "testosterone replacement therapy"; AND "menopause+"	47
PubMed Filters: 2000-2018 English language	"female sexual dysfunction"; AND "testosterone"; AND "drug therapy"; AND "menopause";	96
		After removing duplicates 172 unique articles

Appendix 2

Evidence-Informed Recommendations

Diagnosis

- HSDD remains a diagnosis in clinical research and clinical practice despite DSM-5 transition to FSIAD. A clinician will need to evaluate which approach to use guided by patient presentation and the principle that over diagnosis of sexual dysfunction is a professionally recognized concern and should be avoided.
- A thorough evaluation of potential biopsychosocial contributions to the diagnosis is essential and testosterone therapy can be considered if other factors are not thought to contribute significantly.

Prescription

- Consider non-pharmacological options prior to prescribing testosterone.
- A transdermal testosterone cream is the best evidence supported route of delivery, and 5 milligrams daily is an appropriate starting dose.
- Prescription of a commercially manufactured male 1% formulation would avoid issues such as inconsistent purity, concentration, and bioavailability associated with compounded products.
- Accurately varying the amount of a 1% testosterone cream can be achieved by use of a graduated syringe or other dispensing devices such as Topi-Clic®.
- Product information for Androfeme 1%, a female testosterone cream licensed for use in Australia, provides details on testosterone therapy specific to women. This content may be useful to review and share with patients as available testosterone monographs in Canada are related to male testosterone use.
- If compounded cream is prescribed, concerns with product consistency might be minimized if the patient reliably uses the same compounding pharmacy.
- Concerns associated with off-label and/or compounded medication use need discussion and documentation in the patient's medical record.

Adverse Effects

- Patients should be informed that increased unwanted hair growth or mild acne are the most likely adverse effects and should be assessed for.
- Patients should be informed that more serious adverse effects such as virilization, or breast cancer are not thought to be associated with therapy, but long-term clinical evidence is insufficient to rule them out.
- A woman should be counselled to be familiar with her own breasts, and to be vigilant and seek care with any breast changes.
- Based on recommendations for HRT, testosterone therapy does not warrant increased frequency of mammogram screenings.

Monitoring Testosterone

- Supratherapeutic testosterone is thought to increase risk. Therefore, bloodwork needs to be monitored to keep the serum level in the normal therapeutic range.
- An appropriate laboratory panel would be "bioavailable testosterone" which includes total testosterone, free testosterone and sex hormone binding globulin.
- The upper normal premenopausal physiologic range of free testosterone is the therapeutic target.
- Titration up to this therapeutic target is not necessary if the woman is satisfied with her response at lower serum levels.
- An appropriate assessment of initiation would involve ordering baseline testosterone levels; levels after three weeks and making dose adjustments if needed; levels in another 3 weeks, and then a clinical appointment for evaluation of efficacy and adverse effects at around 7 weeks after initiating therapy.
- Reference ranges are known to vary by assay, consequently a consistent laboratory service should be utilized.
- When stable levels are achieved it is recommended that bloodwork should still be checked every six months for safety. However, if custom compounded creams are used then bloodwork would be required 3 weeks after beginning a new batch of compounded cream. Essentially, this requires monthly bloodwork as compounded creams have a beyond-use-date of 30 days after compounding.
- Any change to oral estrogen dose, or formulation, may influence SHBG levels. Additional bloodwork would be required to ensure that serum testosterone levels remain in the target range.
- Elevated SHBG can decrease free testosterone even while total testosterone trends to supraphysiologic levels. Factors that elevate SHBG should be investigated rather than further increasing the dose of testosterone in order to fractionally increase free testosterone levels.
- Consider changing estrogen therapy from a CEE preparation to a non-CEE estrogen as the effect on SHBG is less; or to transdermal estrogen as it does not increase SHBG.

Evaluating Benefit

- Any benefit would expect to be seen around 6-8 weeks after beginning therapy, and would plateau around 3 months. If no benefit, the trial should end by 6 months.
- Tools such as sexual desire or sexual distress scales are available for quantitative tracking of therapeutic effect. These scales have only been validated with the HSDD diagnosis.
- Trusting a woman's intrinsic capacity to appraise the value of the treatment would be a qualitative approach supported by literature, and does not require validated tools.
- A composite evaluation of SSE, decreased distress and increased desire, as well as the acceptability of the therapeutic modality including the requisite blood work, and ongoing clinical follow-up would be appropriate.

Duration of Therapy/Discontinuation

- Appropriate duration of therapy is unclear. It may be acceptable to continue therapy if coupled with ongoing evaluation of serum levels and surveillance for adverse effects, as long as the patient is accepting of the ambiguity of risk associated with long-term therapy.
- A more conservative approach of tapering the dose over time, or conducting a discontinuation trial might be more reasonable than indefinite therapy.
- A consultation with a specialist may be warranted for prolonged therapy.
- Distress surrounding lack of sexual desire tends to decrease with age. Therefore, even if sexual desire declines during a discontinuation trial, a woman might be accepting of this, and not having to worry about daily application of cream, ongoing bloodwork, and clinic visits may better align with her contemporaneous values.
- In discontinuing therapy, there is insufficient evidence to recommend either tapering or abrupt cessation. However, tapering would be easy to implement using testosterone cream, and may be preferable.