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Foreword

William F. Rayburn, MD
Consulting Editor

This issue of the *Obstetrics and Gynecology Clinics of North America*, guest edited by J. Chris Carey, MD, deals with the important subject of sexual dysfunction. Most people, women and men, view their sexuality as an important quality-of-life issue. Obstetrician–gynecologists are perceived by many women as the initial contact for exploring all aspects of their health, including their sexuality. If physicians do not respond to these concerns, patients may become discouraged about discussing their sexuality and may have their fears and doubts reinforced. Additionally, accompanying gynecologic disease processes and therapeutic interventions associated with impaired sexual response may go overlooked.

Physicians should perceive their patients' sexual health as being an integral part of life changes. Certain events in a woman's life can prompt her to be concerned about her sexual health. Examples of such events include development of secondary sexual characteristics, sexual activity and intercourse, need for and use of contraception, sexual function, pregnancy, menstruation or menopause, surgery or medications that affect future childbearing, and changes in a marital or intimate relationship.

A nonjudgmental interview should be conducted in a comfortable and private office setting. It is best not to elicit a complete sexual history with the patient in a hospital gown or while she is on an examination table. An obstetrician–gynecologist's immediate task is to reduce the patient's immediate anxiety and to gather sufficient information to make a diagnosis. A rushed response to even the most innocent question of a sexual nature may reinforce that patient's concerns or may contribute to her feelings of

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inadequacy. If there is insufficient time for a relaxed discussion, it is better to listen to the woman for a few minutes, and to reschedule the interview in the near future.

This issue covers such common disorders of sexual dysfunction as a loss of desire, loss of arousal, anorgasmia, vaginismus, and dyspareunia. Sexual dysfunction rarely occurs as a single problem. Therapy involves a series of behavior modifications directed toward teaching the partners about external physical and internal behaviors and about eliminating any emotions that inhibit appropriate responses.

The distinguished group of authors assembled in this issue brings their expertise to describe tools and therapy for sexual dysfunction. Management of sexual problems involves the following components: (1) educating about sexual response cycles and underlying physiology, (2) relieving anxiety and guilt, (3) searching for factors that contribute to low sexual desire, (4) assessing and managing chronic dyspareunia or apareunia, (5) prescribing medications or hormone therapy, and (6) advising caution about certain medicinal or mechanical products for sexual dysfunction. These multifaceted interventions can be complex and may require long-term follow-up. Referral may be a better option for the obstetrician–gynecologist who either is too busy or does not feel sufficiently confident to undertake this treatment.

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Preface

J. Chris Carey, MD
Guest Editor

Sexual dysfunction is one of the most common conditions seen in a primary care provider's office. Large surveys indicate that one fourth or more of patients report sexual distress or dysfunction. Yet the diagnosis is rarely made, even though most patients who have a sexual problem report that they wish their physician would ask about it.

Why do physicians not uncover sexual problems? Many physicians state that they do not know what to do when they uncover a sexual problem. They are afraid that addressing the problem will take too much time and that they do not have anything to offer the patient. They do not have a referral source for therapy or believe that the patient will be resistant to referral to a therapist. Physicians often do not know how to take a sexual history and do not know how to diagnose and treat common sexual problems.

In this issue of *Obstetrics and Gynecology Clinics of North America*, we hope to provide tools that primary care providers can use to address sexual problems. Dr. Kingsberg discusses the elements of a sexual history. Dr. Rosen describes the normal sexual response in women. Dr. Amato explains the types of sexual dysfunctions. Drs. Carey, McGloin, and MacNeil discuss specific disorders in detail. Dr. Bachmann describes androgen insufficiency syndrome, and Drs. Bodurka and Sun discuss the important problem of sexual dysfunction after gynecologic cancer. Finally, I review

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pharmacologic treatment of sexual function and sexual side effects of common drugs.

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Normal Sexual Response in Women

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Sexual response in women is highly variable and multifaceted, including a complex interplay of physiologic, psychologic, and interpersonal components. Although common elements and pathways have been identified, the role of individual differences, learning factors, and sociocultural influences on women's sexual response cannot be overstated. Despite major advances in understanding of the neurobiology and pharmacology of sexual response, defining normal sexual response in women remains highly challenging and controversial. Early sex researchers, such as Alfred Kinsey [1] and Masters and Johnson [2], observed a high degree of variability in sexual response patterns among their female subjects. This observation has been confirmed repeatedly in survey and laboratory studies during the past two decades. New models and theoretical concepts have been proposed recently to account for this variability in female sexual response [3,4], which is reviewed later in this article.

Given the complex and highly variable nature of sexual response in women, it is not surprising that little consensus exists currently on the definition of "normal sexual response." Although various definitions of female sexual dysfunction have been proposed, these definitions typically fail to define or describe the essential characteristics of normal sexual response in women. Rather, normal response is defined in most epidemiologic or clinical studies by the absence of overt sexual dysfunction [5]. Significant problems with this approach are (1) the need for a positive definition of female sexual response, and (2) lack of consensus concerning the definition and criteria for sexual dysfunction in women. Research and practice in this area have been significantly limited by these difficulties.

How important or necessary is sexual response to adequate physical or mental health in women? This is another major area of controversy at

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present. Recent survey studies show that most men and women rate an adequate sex life as important to their overall happiness and relationship satisfaction [5]. More than 60% of women in one survey stated that having an adequate sex life was integral to their physical and emotional satisfaction. Although these surveys indicate that sex is an important source of personal and relationship satisfaction for most women, there is a significant minority of women (approximately 40% in most surveys) who do not rate sex as important for their emotional or physical well-being. These findings have led to a strong emphasis on personal or interpersonal distress as a necessary component of the definition of sexual dysfunction in women.

Finally, the role of cultural and ethnic differences is essential to the definition. Major differences exist from one culture to another in the way sexual response in women is viewed and the expectations for normal female sexuality. These expectations vary from highly positive in most western cultures to highly negative in traditional Asian or African cultures. In fact, female genital circumcision continues to be practiced in many parts of Africa as a means of limiting or controlling sexual pleasure in women. Furthermore, taboos or restrictions regarding sex during menstruation, pregnancy, or menopause greatly impact sexual response in women in many societies. Direct communication about sexual issues may be more or less acceptable from one culture to another, making it difficult for women in more traditional cultures to express their sexual needs to their partners or to initiate discussion about sexual difficulties. Women from traditional cultural or religious backgrounds may similarly experience difficulty in seeking professional help for a sexual problem or dysfunction.

In summary, normal female sexuality is highly variable from one individual and culture to another. Although aspects of sexual response, such as vaginal lubrication and orgasmic contractions, seem to be near-universal and occur reflexively in sexually functional women receiving adequate sexual stimulation, the subjective or emotional aspects are highly individual and subject to learning and cultural factors. Female sexuality is essentially malleable, as the importance of individual experience and learning factors has been observed in many studies. Although normal sexual response in women is often defined by the absence of dysfunction, limitations of this approach have been noted. Social and cultural factors also play an important role in shaping expectations regarding normal sexual response in women. This article reviews traditional medical models and concepts of sexual response and highlights recent developments in the field.

Changing concepts and scientific perspectives

Major advances have occurred in understanding of sexual physiology and pharmacology in men and women, including the role of steroid hormones and central neurotransmitters and the importance of psychologic and interpersonal factors. Recent models have emphasized the need for integration of

physiologic and psychologic determinants. Looking back 50 years, there has been a progressive growth of knowledge and understanding about normative sexual behavior in women (and men). Three major sources of data have contributed to this growth in knowledge.

Epidemiologic and large-scale survey studies

Epidemiologic and large-scale survey studies have provided normative data about changes and variations in sexual behavior over the life cycle and about the role of demographic, biomedical, and social factors in shaping sexual behavior in men and women. The first large-scale survey study of sexual behavior in women was conducted in the early 1950s by Kinsey and colleagues [1], whose groundbreaking study contributed many insights regarding normal female sexuality and paved the way for future studies of sexual behavior in men and women. Among Kinsey's major contributions are the similarities and relevance of orgasm in male and female sexual response, the importance of foreplay and adequate sexual stimulation in women, and the role of masturbation in sexual development. Recent surveys have confirmed many of Kinsey's earlier findings, in addition to highlighting the variability in sexual response and wide range of subjective responses associated with sexual arousal and orgasm in women [6].

Laboratory psychophysiologic studies

Laboratory psychophysiologic studies in women have contributed greatly to understanding the processes of sexual arousal and response in men and women. These studies have highlighted the role of individual differences and variability in sexual response and the importance of cognitive and subjective factors in sexual response. New models have been proposed for understanding the interaction between physiologic and psychologic processes in particular. These newer models are discussed later in this article.

Basic science paradigms and animal models

Basic science paradigms and animal models have recently been developed for investigating neurophysiologic and pharmacologic mechanisms in female sexual response and the effects of sex steroid hormones on different components of female sexual response. Despite the potential value of these models in understanding physiologic mechanisms, the relevance and generalizability to sexual response in human females is uncertain and requires further investigation.

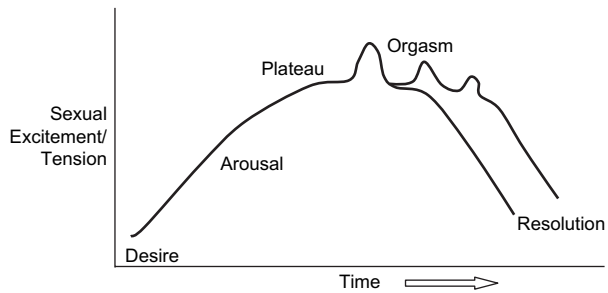
Given the accumulation of new knowledge from each of these approaches, scientific perspectives on sexual response in women have undergone major changes in recent years. In particular, new models of sexual response in women have been proposed that are considered in detail in this article. These models provide a conceptual framework for understanding the sequence of

physiologic events and psychologic processes that comprise normal sexual response for most women. None of the models to date, however, have been shown to be universally applicable and each model has important drawbacks and limitations.

The Masters and Johnson (four-stage) model

Based on their laboratory observations of sexual response in approximately 700 men and women, Masters and Johnson [2] proposed a four-stage model of sexual response (Fig. 1). The Masters and Johnson model described an orderly sequence of physiologic responses, beginning with sexual excitement and culminating in orgasm and resolution in both men and women. The model includes the well-known phases of excitement, plateau, orgasm, and resolution, each of which has associated genital and extragenital responses. According to the model, sexual response involves a gradual build-up of sexual tension in both sexes, followed by the release of orgasm. Some women, it was noted, are capable of multiple orgasms before resolution. The Masters and Johnson model has been widely accepted and has formed the basis for most subsequent conceptualizations of sexual response in men and women. The model was also used as a framework for understanding common problems and sexual dysfunction in men and women [7].

According to this model, excitement is the first phase of sexual response. In women, this is characterized by increasing pelvic vasoengorgement and vaginal lubrication in adequately estrogenized women. Masters and Johnson also described a wide range of extragenital responses occurring during



Adapted from: Masters W. H. & Johnson, V. E. *Human Sexual Response*. Boston, Mass: Little Brown & Co.; 1966.

Fig. 1. Based on their landmark research of the 1960s, Masters and Johnson developed a linear four-phase model of sexual response: excitement, plateau, orgasm, and resolution. Kaplan proposed an alternate model in 1979 and introduced the concept of desire into normal sexual responses. In this model, desire leads to arousal, then plateau is followed by orgasm and resolution. This model was intended to reflect sexual response for males and females; however, researchers have recognized that some women did not experience all four phases of the cycle. As such, this model has been criticized, because it does not reflect a woman's actual experiences. (*Adapted from* Masters WH, Johnson VE. Human sexual response. Boston: Little Brown & Co.; 1966.)

sexual excitement, including flushing, nipple engorgement, muscle tension, and changes in heart rate, blood pressure, and respiration. These extragenital responses are highly variable from one woman to another. Subjective arousal and mental involvement also increase with increased stimulation. In the sexually functional woman, a high level of sexual excitement is maintained during the plateau phase as the orgasmic platform develops. With increasing vasocongestion and muscle tension in the outer third of the vagina, rhythmic, involuntary contractions are elicited, resulting in female orgasm. For most women, this is associated with intense subjective feelings, and a brief loss of consciousness (*petit mort*) even occurs in some women. No distinction is made, according to the Masters and Johnson model, between vaginal and clitoral orgasms in women or orgasm induced through any other form of stimulation. Following one or more orgasms, a gradual return to the pre-stimulated state (resolution) occurs.

Despite the enormous influence of the Masters and Johnson model, several limitations and criticisms have been noted [8]. First, the model assumes a linear progression of increasing sexual excitement from the onset of stimulation to orgasm and resolution. In this respect, the model fails to adequately describe the highly variable patterns of response seen from one woman to another or even the variability in response from one episode to another in the same woman. The model is also focused predominantly on the physiologic aspects of sexual response and does not reflect the importance of subjective, psychologic, or interpersonal aspects of sexual response. Finally, the model assumes that a sexually functional woman is always responsive to sexual initiation or stimulation, and no indication is given of the importance of sexual desire or libido in their model.

The three-stage model

To address this latter deficiency, a three-stage model of sexual response was proposed by Helen Singer Kaplan [9]. According to this model, the sexual response cycle was reconceptualized as consisting of three essential phases: desire, excitement, and orgasm. Kaplan's first stage of sexual desire consists of physiologic and psychologic components of sexual desire or libido, which are mediated by brain centers in the limbic system but are also influenced to a degree by hormonal (ie, androgenic) and psychosocial influences. The desire phase is viewed as a necessary precursor to the development of adequate excitement and subsequent orgasm in men and women. Although desire is described as centrally mediated, excitement and orgasm are peripherally-based processes primarily mediated by centers in the spinal cord.

Kaplan's three-stage model was used as the basis for classification of male and female sexual dysfunction in the third and fourth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IV). According to this model, sexual dysfunctions in men and women are divided into disorders of sexual desire (hypoactive sexual desire disorder), sexual

excitement disorders (male erectile dysfunction, female sexual arousal disorder), and orgasmic disorders (premature ejaculation, male and female anorgasmia). The model has been highly influential in shaping current conceptualizations of normal and dysfunctional sexual response in men and women, although it is subject to many of the limitations of the original four-stage model of Masters and Johnson. In particular, both models are based on the assumption of a linear and largely invariable progression of sexual response with parallel processes in men and women. Newer models emphasize the variability in response from one individual or situation to another and nonlinearity that may characterize normal sexual response in women.

Circular models of female sexual response

In response to the inadequacy of the traditional Masters and Johnson [2] and Kaplan [9] models of sexual response in reflecting women's experiences of sexual response, newer conceptualizations have been proposed to explain normal sexual response in women. Prior models used a linear progression through the stages of sexual response and lacked a focus on psychologic or interpersonal issues. Current models address these limitations and go further in advancing a conceptualization of healthy female sexual response that is consistent with the qualitative and subjective experiences of women.

An initial departure from this traditional linear model of sexual response was proposed by Whipple and Brash-McGreer [10], who described a circular model of sexual response. This model included the phases of seduction (including desire), sensations (excitement and plateau), surrender (orgasm), and reflection (resolution). By shifting to a circular model, Whipple and Brash-McGreer proposed that satisfying sexual experiences are likely to have a reinforcing effect on women, making them more likely to desire sex, or conversely, to lose desire for sexual activity if their sexual experiences are unpleasant or negative. More specifically, reflection on the sexual experience as pleasurable can lead to the seduction phase of the next sexual encounter. This model therefore acknowledged the cyclic nature of women's sexual response, although the process of change throughout the various phases in this response cycle did not differ substantially from that in the previous linear model. Moreover, the particular phase descriptions of seduction, sensation, surrender, and orgasm have not been widely accepted as independent phases of female sexual response.

The most widely cited current model of female sexual response, Basson's intimacy-based model, also conceptualizes female sexual response as cyclic in nature (Fig. 2) [3,11]. This model of female sexual response, however, departs from the traditional elements of desire, excitement, plateau, orgasm, and resolution, arguing that these are not reflective of women's sexual experiences. The Basson model is based on observations that women experience the phases of sexual response in an overlapping, nonsequential manner that incorporates mental and physical components [3,12].

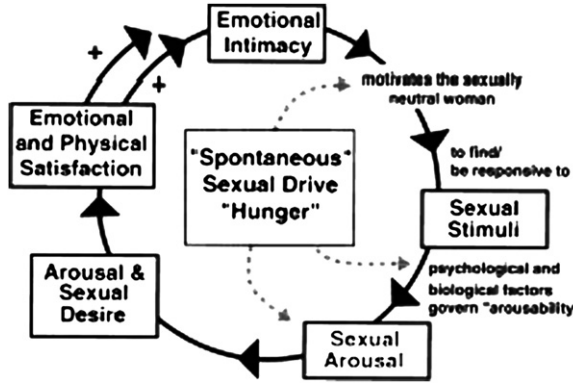


Fig. 2. Basson's intimacy-based model of female sexual response cycle. (*From* Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 2001;98:350–3; with permission.)

An important new concept in this model is that the desire for sex does not necessarily precede sexual stimulation or arousal. According to Basson's model, women frequently enter into a sexual experience through a stance of neutrality with positive motivation for intimacy or relationship. Rather than initiate sexual activity out of sexual drive, as the traditional model would propose, a woman may instigate physical contact or be receptive to sexual initiation for various reasons, such as the desire for closeness, intimacy, commitment, and as an expression of caring. Findings from a large, longitudinal study on premenopausal women found that women cited various reasons for engaging in sexual activity, including her partner's desires and wanting to relieve physical or emotional tension [13]. This model thus seems at least somewhat consistent with empiric data regarding the motivations of women to engage in sexual activity.

A unique aspect of this model is thus its consideration of sexual desire, in that spontaneous desire, including sexual thoughts, feelings, and fantasies, is viewed as one potential component of the sexual response cycle, but that is not necessary for sexual excitement or orgasm to occur. In this model, spontaneous desire may contribute to the woman's willingness to become receptive or to her psychologic and biologic processing of the sexual stimuli [3]. A lack of spontaneous sexual desire in this model, however, is considered normal rather than dysfunctional, in contrast with traditional models of sexual response [11]. This aspect of the cycle is also supported by literature finding a high prevalence of low desire in women [5] and the use of fantasy as a strategy to maintain arousal rather than as a sign of desire [14].

In Basson's model, arousal is conceptualized as a process that is influenced by biologic and psychologic factors. This model assumes that simply because a woman is involved in sexual activity and stimulation does not mean she is necessarily aroused; her ability to be aroused (her

"arousability") [15,16] may be influenced by factors such as fears of sexually transmitted disease, past negative sexual experiences and abuse, inadequate birth control, and low self-image. Given positive circumstances and adequate stimulation, a woman is able to focus on the sexual stimulation she experiences. In this model, the type of stimulation, the time needed to become aroused, and the context in which arousal occurs are all highly individual [3]. As a woman's sexual pleasure grows and intensifies, she begins to feel desire for sex in a reciprocal fashion. Experiencing arousal may lead to sexual satisfaction and nonsexual rewards, such as emotional intimacy and well-being, both of which create continued motivational incentives for engaging in sexual activity. The notions of arousal and desire as reciprocal processes are echoed in previous writing regarding the connectedness of arousal and desire and experimental findings supporting the importance of psychologic factors in arousal in women [17].

Another contrast with the traditional model of female sexual response is that orgasm and resolution are not essential in Basson's model of the sexual response cycle [3]. Sexual satisfaction is viewed as occurring when a woman is able to focus on her sexual pleasure without negative outcome, such as pain, yet it may occur with or without orgasm. This emphasis on the subjective nature of sexual satisfaction as opposed to an objective endpoint like orgasm may be more consistent with women's varied sexual experiences. Basson also emphasizes that women have many reasons for engaging in sex, and that these reasons (the desire for emotional intimacy, for example) may have little or nothing to do with feelings of sexual desire. Further, she describes a potential "disconnect" between a woman's feelings of sexual arousal and the physiologic changes, such as genital vasocongestion, that typically accompany sexual arousal. Basson's model of the sexual response cycle is circular and includes the multiple sexual and nonsexual reasons for engaging in sex, the psychologic and biologic influences on arousability, and subjective feelings of arousal and desire. Within this model there are many factors that may instigate sex and various potential positive outcomes resulting in a range of sexual response cycles in different women. Factors that may interfere with a satisfactory cycle include minimal emotional intimacy, lack of appropriate sexual stimuli, negative psychologic factors, such as distraction and fear, and fatigue, depression, or medication effects that reduce arousability. According to Basson, "It may well be that the women's 'dysfunction' is logical and adaptive but can still cause serious personal and interpersonal distress and require assessment and management" [3].

Basson's model offers new insights into normal sexual response in women. Subjective arousal plays a central role in her conceptualization. Feelings of subjective arousal or emotional involvement do not always correlate with physiologic measures of genital congestion. Indeed, emotions and thoughts have a stronger influence on the subjective experience of sexual excitement than does feedback from genital vasocongestion. It is also possible for a woman to experience healthy sexual vasocongestion or genital

lubrication with minimal or no feelings of sexual arousal or excitement. The model also incorporates biologic, psychologic, and contextual factors in a more comprehensive framework. Finally, the model acknowledges the reciprocal relationship between arousal and desire in women while discounting the previously held notions regarding the primacy of spontaneous sexual desire in women and the necessity of orgasm as a clinical endpoint. These features set the current model apart from previous models of sexual response and may make it more reflective of women's actual day-to-day sexual experiences.

Despite its significance, there are important limitations of this model that need to be recognized. First, it is based largely on clinical observation and lacks experimental verification. In addition, it could be argued that the shift toward viewing sexual desire in women as often receptive or responsive in nature may reinforce negative stereotypes of women as sexually passive or unassertive. Moreover, the model is largely intimacy-based and may exclude some women whose sexual desires and arousal are not intimacy-linked. Nevertheless, by shifting the focus to include subjective and interpersonal factors and by recognizing the nonlinear nature of women's sexual experience, Basson's model has contributed greatly to the current understanding of healthy sexual response in women.

Laboratory studies: further evidence of disassociation

A core feature of the circular model is the potential for certain components of sexual response, such as vaginal vasocongestion and subjective arousal, to occur in different sequences or combinations, or even to be disassociated in normal women. In other words, normal women have the capacity to experience vasoengorgement or vaginal lubrication (or other extragenital responses) without the subjective perception or experience of sexual excitement or vice versa [8]. For the past 20 years, psychophysiologic studies in several laboratories in Europe and the United States have demonstrated the potential for disassociation or discorrelation of these components of sexual response in women in various experimental settings and subject populations [18]. Although in men reports of subjective excitement and increases in penile engorgement are characteristically highly correlated, women's perception or subjective arousal may or may not match their state of physiologic arousal. In one set of recent studies, for example, women's physiologic arousal was found to be nonspecific with regard to the eliciting sexual stimulus, in that normal heterosexual women showed substantial physiologic arousal as measured by way of vasoengorgement of the genitals to representations of preferred and nonpreferred genders [19]. In these studies, women also show physiologic arousal to nonpreferred sexual activities, such as depictions of a sexual threat [18]. This is in stark contrast with the responses of men, who show category-specific arousal in that normal men usually show greater physiologic arousal to representations of the preferred

gender and sexual activities. Moreover, pharmaceutical agents designed to increase vasocongestion in women typically have little or no effect on subjective arousal [20], providing further evidence for the lack of association between physiologic and psychologic arousal in women. This may be one of the key reasons for lack of effectiveness of phosphodiesterase type-5 (PDE-5) inhibitors in women.

Chivers and colleagues [4,19] recently investigated the stimulus specificity of sexual arousal in men and women by means of a series of well-controlled experimental studies, and their findings offer increasing evidence for the lack of specificity in women's genital arousal. For example, Chivers and Bailey [4] examined the effects of different types of erotic stimuli on genital and subjective arousal in 36 heterosexual men and women. In this study, male and female participants viewed several categories of erotic films while their physiologic arousal was measured by way of penile plethysmograph recording in the men or vaginal pulse amplitude measures in the women. The specific stimuli included film clips of female–female, female–male, and male–male contact in oral and penetrative sexual activities. Subjects also viewed film clips of female and male chimpanzees engaging in repeated penile–vaginal sex or neutral clips of landscapes or chimpanzees engaging in a nonsexual activity. Results of the study showed marked discordance between the women's subjective and physiologic responses to the films. Surprisingly the women showed significant physiologic arousal to the same-sex and animal-sex scenes, despite negative subjective responses to these stimuli. In contrast, men's physiologic arousal was more concordant with their subjective ratings of arousal. Men showed significantly less genital arousal to the male–male clip than to the female–male clip, suggesting category-specific arousal, and they showed a complete absence of physiologic or subjective arousal to the scenes of nonhuman sexual activity.

The findings are interpreted by Chivers and colleagues [4] as evidence of a fundamental gender difference in patterns of physiologic and subjective response to sexual situations. Specifically they propose that women have greater physiologic responsiveness to category nonspecific stimuli (eg, nonpreferred gender or sexual activity) than men, although women's subjective appraisal and emotional responses are strongly tied to their preferred category or type of sexual stimulus. The pattern of physiologic and subjective arousal is much more highly correlated or consistent in men. Chivers and colleagues hypothesize that this predisposition toward disassociation of physiologic and subjective components of sexual response in women may serve important adaptive functions, because the physiologic responses of vasoengorgement and vaginal lubrication are protective against injury of the women's reproductive organs in coercive or unwanted sexual encounters. Further research is clearly warranted to investigate this interesting and provocative new hypothesis. Whatever the explanation, these and other findings from laboratory studies in women highlight the range and variability in patterns of sexual arousal in normal women.

Summary

In summary, women's sexual response is characterized as highly variable and influenced by a wide range of determinants, including physiologic, psychosocial, and contextual factors. This complexity is reflected also in the multiple etiologic factors and determinants of sexual problems in women. It is evident in current conceptualizations of normal female sexual response, as presented in this article, in which the circularity and overlap of different components and aspects of sexual response in women are viewed differently from the more linear and invariable trajectory of sexual response in men. It is not surprising, therefore, that treatments that target limited physiologic aspects of women's sexual response, such as PDE-5 inhibitors and other vasoactive agents, have demonstrated little overall effectiveness in treating women's sexual dysfunctions [21,22]. Rather there is consensus at present regarding the need for a more holistic or biopsychosocial approach to management of sexual dysfunction in women. Clearly the roles of psychologic and interpersonal determinants need to be taken into account in this approach. Perhaps most important and especially relevant for treating female sexual dysfunction is the emphasis on interpersonal factors as contributors to the ultimate sexual satisfaction of women. Clinicians should be especially mindful of this influence when addressing women's sexual problems.

Another implication of this research is the need for broader definitions and conceptualization of sexual dysfunction in women. Current diagnostic definitions of female sexual dysfunction are based largely on the traditional sexual response cycle models of Masters and Johnson [7] and Kaplan [9]. With the development of new models and concepts of normal sexual response in women, it is increasingly necessary for new definitions and concepts of sexual dysfunction to be developed. Promising efforts have been made in this regard, although much work remains to be done.

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Categories of Female Sexual Dysfunction

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Normal female sexual function

Female sexual function is complex and influenced by a multitude of factors. Until recently, little research has focused on female sexuality. One limitation to advances in the field has been the absence of a well-characterized diagnostic classification system.

Traditionally the female sexual response cycle has been based on a model proposed by Masters and Johnson in the 1960s [1]. This model proposed a linear progression through four phases: excitement, plateau, orgasm, and resolution. This model was later modified by Kaplan to include a three-phase model consisting of desire, arousal, and orgasm [2]. This model forms the basis of the DSM-IV classification of female sexual dysfunction [3].

More recently, however, in recognition that different aspects of the female sexual response may overlap and feed back on each other, Basson has proposed a more circular model that includes emotional intimacy and physical satisfaction as goals [4] (Fig. 1). This model takes into account the various physiologic/organic and psychologic factors that may influence the female sexual response and the fact that women may engage in sex for various reasons. Central to the model is also the concept of receptive sexual desire. Although spontaneous desire may occur less often in women compared with men, women can often enter the sexual response cycle and desire can be triggered by various factors, providing the woman is receptive to these cues.

Prevalence of female sexual dysfunction

Because of the general lack of understanding about the female sexual response cycle and the lack of standardized definitions until recently, there

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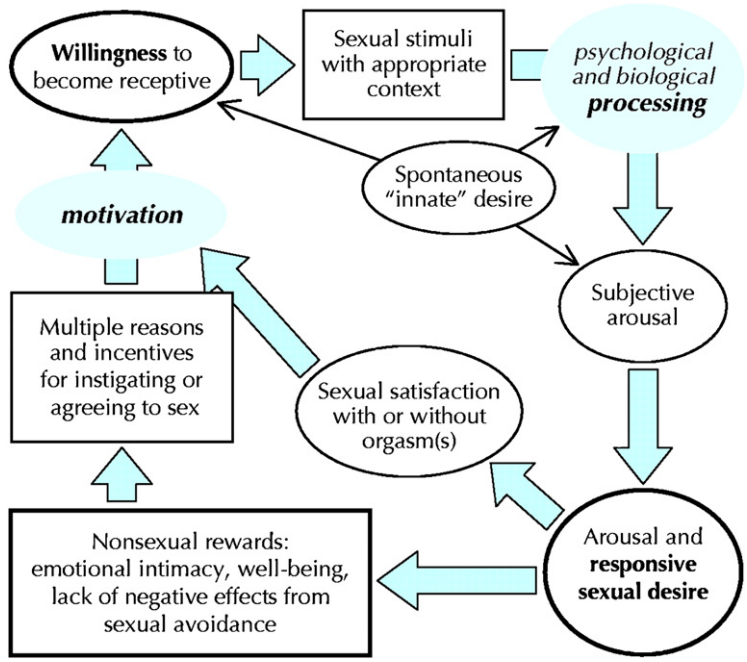

Fig. 1. Model of the female sexual response cycle. (*Adapted from* Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 2001; 98:350–3; with permission.)

exists some controversy regarding the exact prevalence of female sexual dysfunction. In the most frequently quoted study based on the National Health and Social Life Survey of 1992, which evaluated a sample of 1749 women aged 18 to 59 years, 43% reported sexual dysfunction [5]. Low desire was the most common complaint.

Physiology of the female sexual response

The physiology of the female sexual response refers to the genital vasocongestive and neuromuscular events that occur along with the subjective arousal and the associated somatic responses. A discussion of the complex neurogenic regulation of female sexual function is beyond the scope of this article [6,7]. Spinal and central pathways are involved. Within the central nervous system, the medial preoptic, anterio-hypothalamic, and limbo-hippocampal areas have been shown to play important roles in the female sexual response. These areas then transmit signals by way of the peripheral nervous system to modulate the vasculogenic and musculogenic aspects of the female sexual response. Various neurotransmitters and neuropeptides

are believed to modulate sexual function. In addition, the sex steroid hormones likely influence these pathways.

During sexual arousal, genital vasocongestion occurs as a result of increased blood flow. Sexual arousal is characterized by labial engorgement, increased vaginal lubrication, vaginal lengthening and dilatation, and increased length and diameter of the clitoris.

The pelvic floor muscles, particularly the levator ani and perineal membrane, and the smooth muscle of the vagina participate in the female sexual response.

Mediators of the female sexual response

Neurotransmitters and neuropeptides

Neurotransmitters and neuropeptides, such as serotonin, dopamine, epinephrine, norepinephrine, histamine, opioids, and gamma-aminobutyric acid (GABA), are believed to modulate sexual function [6]. Genital engorgement is associated with parasympathetic vasodilation mechanisms, primarily mediated by nitric oxide (NO), acetylcholine, and vasoactive intestinal peptide (VIP). Immunohistochemical studies have confirmed the presence of various neurotransmitters in human vaginal and clitoral tissues, such as neuropeptide Y (NPY), VIP, NO, calcitonin gene-related peptide (CGRP), and substance P [8]. Contraction of the vaginal and pelvic floor muscles likely involves adrenergic and cholinergic mechanisms from efferent pudendal nerves.

Sex steroid hormones

Estrogen plays a role in maintaining the integrity of the vaginal tissues. Menopause is associated with atrophy of the vagina and postmenopausal women often complain of vaginal dryness and associated dyspareunia [9]. Low estrogen levels have been shown to be correlated with female sexual dysfunction [10].

Although serum testosterone levels correlate poorly with female libido, testosterone is nonetheless believed to play an important role in female sexual desire. Androgen insufficiency syndrome is characterized by a diminished sense of well-being, fatigue, and decreased libido [11]. Androgen levels decrease as a woman ages [12]. The postmenopausal ovary continues to secrete androgens. Bilateral oophorectomy, however, (or surgical menopause) is associated with much more dramatic decreases in androgen levels compared with spontaneous menopause [13,14]. Recent studies suggest that testosterone therapy in the form of a transdermal patch may improve libido in postmenopausal women who have hypoactive sexual desire disorder [15–19]. Currently, however, there are no Federal Drug Administration (FDA)-approved androgen therapies for the treatment of female sexual dysfunction.

Table 1
Factors influencing female sexual function[a]

Biologic/physiologic factors
Neurologic disease
Cancer
Urologic or gynecologic disorders
Medications
Endocrine abnormality
Psychologic factors
Depression/anxiety
Prior sexual or physical abuse
Substance abuse
Interpersonal factors
Relationship quality and conflict
Lack of privacy
Partner performance and technique
Lack of partner
Sociocultural factors
Inadequate education
Conflict with religious, personal, or family values
Societal taboos

[a] Adapted from www.femalesexualdysfunctiononline.org/slides. Accessed October 2006.

Factors that influence the female sexual response

Many biologic and psychologic factors influence female sexual function, including biologic, psychologic, interpersonal, and sociocultural factors (Table 1).

Biologic factors

Physiologic conditions that interfere with any of the mediators of the female sexual response may result in female sexual dysfunction. For example,

Table 2
Classification of female sexual dysfunction[a]

Hypoactive sexual desire disorder
Sexual aversion disorder
Arousal disorder
Subjective arousal disorder
Genital arousal disorder
Combined arousal disorder
Orgasmic disorder
Sexual pain disorders
Vaginismus
Dyspareunia
Other sexual pain disorders

[a] Based on American Foundation of Urological Disease definitions.

certain chronic diseases, spinal cord injury, and bilateral oophorectomy may be associated with female sexual dysfunction [20]. Medications such as oral contraceptive pills have also been implicated in female sexual dysfunction.

Psychosocial and interpersonal factors

Depression is strongly associated with female sexual dysfunction [21]. In addition, sexual dysfunction is a common side effect of antidepressants, particularly certain serotonin reuptake inhibitors (SSRIs) [22]. A woman's emotional relationship with her partner and general emotional well-being are predictive of lack of distress about sex [23]. Anxiety, fatigue, a history of sexual abuse, expectations of a negative experience, concerns about safety, and lack of privacy can also contribute to female sexual dysfunction [24,25].

Definitions

In 1998 an interdisciplinary international consensus panel of experts in female sexual function was convened to evaluate and revise the existing classification and definitions of female sexual dysfunction. This resulted in a revised American Foundation of Urological Disease (AFUD) classification system that was published in 2000 [26]. These definitions were subsequently revised and further expanded [27,28,29]. The AFUD classification of female sexual dysfunction is shown in Table 2. The classifications may be subtyped as lifelong versus acquired, generalized versus situational, and organic versus psychologic or mixed. The etiology may be multifactorial and disorders may overlap. An important component of the diagnostic criteria is that the problem must cause personal distress.

Hypoactive sexual desire disorder

Hypoactive sexual desire disorder is the persistent or recurring deficiency or absence of sexual fantasies or thoughts or receptivity to sexual activity that causes personal distress.

Sexual aversion disorder

Sexual aversion disorder is the persistent or recurring phobic aversion and avoidance of sexual contact, which causes personal distress. It is often secondary to a history of physical or sexual abuse or trauma.

Sexual arousal disorder

Sexual arousal disorder is the persistent or recurring inability to attain or maintain sufficient sexual excitement, causing personal distress. Genital lubrication or swelling and subjective sexual arousal are not necessarily correlated. Sexual arousal disorder hence may be further subclassified as

subjective, genital, or combined. Subjective arousal disorder is characterized by absent or reduced feelings of sexual arousal, despite the occurrence of vaginal lubrication and genital swelling. Genital arousal disorder is characterized by lack of vaginal lubrication or genital swelling, despite feelings of subjective arousal. Combined sexual arousal disorder is characterized by absence of subjective arousal and absence of genital arousal.

Orgasmic disorder

Orgasmic disorder is the persistent or recurrent difficulty in, delay in, or absence of attaining orgasm after sufficient sexual stimulation and arousal, which causes personal distress.

Sexual pain disorders

Dyspareunia

Dyspareunia is recurrent or persistent genital pain associated with sexual intercourse.

Vaginismus

Vaginismus is recurrent or persistent involuntary spasms of the musculature of the outer third of the vagina that interferes with vaginal penetration and causes personal distress.

Other sexual pain disorders

Other sexual pain disorders include recurrent persistent genital pain induced by noncoital sexual stimulation. This may include inflammatory or anatomic conditions, such as vestibulitis or prior trauma.

Clinical evaluation

Evaluation of female sexual dysfunction usually involves an interview of the couple and each partner separately. The evaluation should include a complete medical, psychosocial, and sexual history and physical examination, including a gynecologic examination. Several validated self-assessment questionnaires are available to evaluate female sexual function [30].These can also be used to monitor response to treatment.

Occasionally the evaluation may warrant a pelvic ultrasound or endocrine evaluation, including thyroid stimulating hormone (TSH) and prolactin (PRL) levels. Measurement of sex steroid levels, such as estrogen and testosterone, is seldom useful. Estrogen and testosterone deficiency can often be surmised from history and physical examination alone. Furthermore, commercially available testosterone assays are not sufficiently sensitive for the measurement of low levels of androgens found in women.

Objective measures of genital blood flow, such as vaginal photoplethysmography, and imaging techniques, such as functional magnetic resonance

imaging (fMRI), are currently limited to the research setting. There is a poor correlation between objective measures and subjective arousal.

Therapy largely depends on the etiology and is discussed elsewhere in this issue, but it often involves education, psychotherapy, behavior modification, and occasionally pharmacotherapy. A multidisciplinary approach is ideal.

Summary

Female sexual dysfunction is a complex and common problem. Several factors influence female sexual function, including biologic and psychosocial factors. Evaluation of female sexual dysfunction should include a complete medical and psychosocial history and a physical examination. Treatment should be multidisciplinary and depends on the etiology but may include education, psychotherapy or sexual therapy, and in some cases pharmacotherapy. Further research in this area will likely lead to a better understanding of the physiology of female sexuality and to novel therapies for female sexual dysfunction.

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Taking a Sexual History

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Sexual health: what is it and why is it important to clinicians?

In this post-millennium decade, the topic of sex has moved from the confines of hushed private discussions to an accepted presence in almost all adult public domains (movies, television, literature, office water-coolers, cocktail parties). Yet for all of our public bravado, talking seriously about specific issues of sexuality still creates anxiety in most people. That this discomfort extends to physicians and their patients in a clinical setting creates a significant void in comprehensive health care. According to the World Health Organization (WHO), maintaining sexual health falls under the responsibility of physicians. In 2000, the WHO in conjunction with the Pan American Health Organization (PAHO) published a document entitled *Promotion of Sexual Health* [1]. Included in this document is the following currently accepted definition of sexual health:

> Sexual Health is the experience of the ongoing process of physical, psychological, and socio-cultural well-being related to sexuality. Sexual health is evidenced by the free and responsible expressions of sexual capabilities that foster harmonious personal and social wellness, enriching individual and social life. It is not merely the absence of dysfunction, disease, or infirmity. For sexual health to be attained and maintained it is necessary that the sexual rights of all people be recognized and upheld.

In addition to defining sexual health, this document also provides recommendations for training physicians in sexual health. Moreover, it specifically

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identifies health professionals specializing in reproductive health as needing more in-depth training in sexuality issues [1].

The aim of this article is to provide clinicians the content and interviewing techniques to effectively take a sexual history and assess current sexual function in women. Other relevant topics for a comprehensive understanding of female sexuality have been covered in subsequent articles in this special issue.

Barriers to discussing sexual health

Despite the WHO call for physicians to take the lead in addressing the sexual health concerns of patients, physicians may not be heeding the call. For example, one recent survey estimated that only 14% of Americans aged 40 to 80 years reported that a physician had inquired about sexual concerns within the past 3 years [2]. In the author's own practice as a psychologist treating women who have sexual problems, I see the consequences of this avoidance almost daily. In fact, recently two typical cases presented to remind me of the real task in writing this article. It is not simply to address the topic of *what* to include in a sexual assessment but to first make the case for *why* physicians should take a sexual history and address the sexual concerns of their patients.

1. A 40-year-old married woman presents for treatment of hypoactive sexual desire. When asked the critical question, "What brings you to me now?" her response was, "It took me 2 years of repeatedly asking my gynecologist and primary care physicians for help with my sexual problem. Finally last month my gynecologist handed me your card and said, 'If anybody can help you with a sexual problem it will be her,' and with that, ended discussion of the topic." The patient's prior efforts to ask for help resulted in her primary care physician actually ignoring the question and pointedly changing the subject as if he had not even heard her speak. Her gynecologist responded to her request for help with low desire by saying, "Well, you look normal down there so your sexual problem isn't caused by that."

2. A 36-year-old single corporate attorney presented with primary vaginismus and concomitant difficulty with pelvic examinations. Over the course of her 18-year history of gynecologic examinations she had seen at least eight physicians, none of whom addressed her complaint of not being able to have intercourse. With regard to her difficulty with pelvic examinations, only one physician took notice. Despite initially mentioning the use of dilators, however, the physician quickly dismissed them and said, "Oh, don't bother. You can just use your fingers." She reported that most physicians simply said, "Just relax." At the end of our first session, with a simple cognitive-behavioral treatment plan established and a set of dilators in her briefcase, she commented, "If only one of those prior gynecologists had said something about treatment options I could have saved 15 years of feeling like a sexual failure."

Although most physicians might agree with the concept that they should assess their patients' sexual health, there are several real barriers that impede discussion of sexual health in a clinical setting.

Insufficient medical education or training

Although physicians are now expected to assess and manage the sexual problems of their patients, undergraduate and postgraduate medical education of human sexuality may be incomplete. Sexual health has seldom been given a high priority in medical education. There is fierce competition among ever-growing content areas for a finite amount of classroom time (eg, content is now expected to include population health, evidence-based medicine, medical ethics, financing, and models of health care delivery). Furthermore, medical school faculties often lack trained sexuality educators despite the recognition of the growing need for better sex education [3]. In a recent survey of North American medical schools, most devote less than 10 hours total during the entire 4-year undergraduate curriculum to sexual health education [4].

Lack of confidence

A natural consequence of minimal training in sexual medicine during undergraduate and residency medical education is a lack of confidence in knowledge and mastery in this area. Physicians understandably are uncomfortable addressing a topic they feel insufficiently trained to manage. Further, many physicians feel too self-conscious to discuss sexuality or worry that they will offend or embarrass their patients. Stead and colleagues [5] found that physicians who were treating women who had ovarian cancer cited their own embarrassment and lack of knowledge as reasons why they rarely discussed sexual issues despite having knowledge that these women are at increased risk for sexual problems.

Underestimation of sexual dysfunction prevalence

Although sexual problems are prevalent in women [6–9], physicians consistently underestimate the frequency of sexual problems in their own patients [10]. This underestimation may well be understood as a self-protective rationalization to avoid addressing an uncomfortable problem area.

Time pressure

Time constraints and concerns about insurance reimbursement are frequent barriers to physicians opening a discussion about sexual concerns. Many physicians are unaware that a simple query about sexual concerns

and one or two follow-up questions need only add 2 to 3 minutes to an appointment. If a more complete sexual history or assessment is warranted, a follow-up visit can be scheduled (and billed appropriately with ICD-9 codes), or a referral to a specialist in treating sexual dysfunctions can be made.

Few perceived treatment options

The absence of any US Federal Drug Administration (FDA)-approved pharmacologic treatments for female sexual dysfunctions contributes to many physicians' sense that they have few treatments to offer. Most physicians are hesitant to use off-label pharmacologic treatments and many may not yet be familiar with nonpharmacologic options such as education and counseling.

Patient discomfort

Although patients would like to be helped with sexual problems, they are unlikely to broach the topic first. They look to the physician to initiate dialog and to give permission to discuss sexual concerns. Only 10% to 20% of women from the National Health and Social Life Survey (NHSLS) reported having sought medical consultation for sexual problems [6]. In the American Association of Retired Persons (AARP)/Modern Maturity Sexuality Study of 1384 Americans aged 45 years and older, only 14% of women reported ever seeking treatment from a health care provider for sexual problems [11]. This small percentage reflects patients' reluctance to bring up the topic, rather than the number of women who have sexual dysfunction. In one study of patients on selective serotonin reuptake inhibitors (SSRIs), only 14% spontaneously reported a sexual dysfunction in contrast with 55% who reported sexual dysfunction when directly asked by the physician [12]. Another study of 887 gynecologic patients found that only 3% spontaneously offered sexual complaints but 19% acknowledged a sexual complaint on direct inquiry [13]. Patient discomfort seems to have more to do with anticipated reactions from their physician than from their own avoidance. In Marwick and colleagues' survey of 500 American adults aged 25 years and older, they found that 68% feared that raising concerns about sexual problems would embarrass their physician and 71% believed their physician would dismiss their concerns [14].

Initial assessment of sexual problems

The following section describes what to include in a brief and in a detailed sexual history. Regardless of how brief or how detailed the initial sexual assessment, there are several communication strategies and skills that enhance the efficiency (ie, keeping it straightforward and brief) and effectiveness (ie, allowing for accurate diagnoses and treatment suggestions).

Opening the door

Making the environment conducive

Many physicians find the most difficult part of assessing sexual function is knowing how, when, and where to address the topic. Establishing rapport and putting patients at ease are critical first steps and in general help to improve overall patient satisfaction. In one survey of 1584 women who received routine gynecologic care at an army medical center, subjects were asked about their experiences discussing sexual concerns with a physician [15]. Box 1 lists what 90% of respondents reported as making it easier to discuss sexual concerns [15].

The physician sets the tone for the conversation. If he or she is therefore comfortable and at ease with sexual terminology and content, patients are more likely to also feel comfortable reporting their sexual concerns. Some physicians may benefit from actually practicing the use of explicit sexual terminology to desensitize to any embarrassment or hesitation. Some words (eg, clitoris, penis, cunnilingus) may be surprisingly more difficult to speak out loud. In addition, finding the correct terminology is also a challenge (too formal and the clinician risks not being understood, but reliance on slang may seem offensive or inappropriate) [16]. Blushing or stammering is a giveaway that the physician is not really comfortable with a given topic. Even body language is important in communication and putting a patient at ease when discussing sexuality. Avoiding eye contact sends a negative message. Sitting is much preferred over standing. Not only does sitting down give the impression that more time has been spent with a patient, but standing (especially with one's hand perched on the door handle) sends the message that the physician is wrapping up a visit and does not really want to address any other issues (ie, sexual concerns) even if a question is posed.

When to take a sexual history/assessment

There are numerous opportunities to screen for sexual problems. Taking even a brief sexual history during a new patient visit is effective. It sends a clear signal that discussing sexual concerns or questions is appropriate

Box 1. What made it easier for patients to discuss sexual concerns

Physician had seen the patient before
Physician knows patient
Physician seems concerned about sexual wellness
Physician has professional demeanor
Physician seems comfortable
Physician seems kind and understanding

and encouraged and is a regular component to all history and physical examinations and implies that sexual function is a necessary content area to cover when obtaining a complete medical history from new patients. Many health-related conditions, life events, or developmental milestones may be associated with the development of some sexual problems, and therefore related office visits are occasions to inquire about changes in sexual function. Basson has listed some of the most common medical and life events that bring women in for such office visits (Box 2) [16].

How to take a sexual history and assess current sexual function

The brief assessment (2–3 minutes). The best time to obtain a sexual history or initiate a discussion of sexual concerns varies depending on the nature of the visit. A sexual history is ideally taken within a review of systems (though not as the initial content area). The discussion should take place in a private setting away from anyone who might overhear, and confidentiality must be assured. The patient should be clothed to eliminate the anxiety, discomfort, and vulnerability that are commonly experienced when sitting in an examination gown [17].

In a realistic attempt to encourage all practitioners to address sexual function in their patients, even the most basic assessment can be useful and can be limited to a minimal number of specific questions with minimal time involvement. Opening the topic by mentioning the importance of assessing sexual function as part of the usual history and physical examination with *all* patients may put patients at ease. The three questions listed in Fig. 1 suffice for the most basic assessment [18].

Although some physicians may be concerned that asking about the gender of patients' partners may not be relevant to some patients and may even put them off, it is an essential question. Not all patients are heterosexual or behave heterosexually (even if they label themselves as such) and it is important not to label patients with preconceived stereotypes. For example, if

Box 2. Office visits that provide opportunities for sexual health screening

Prior to gynecologic surgery (eg, hysterectomy, oophorectomy, uterine prolapse)
Menopause-related visit
Antenatal visits
Postpartum visits
Annual gynecologic examination
Infertility assessment and treatment
Management of chronic illness
Depression

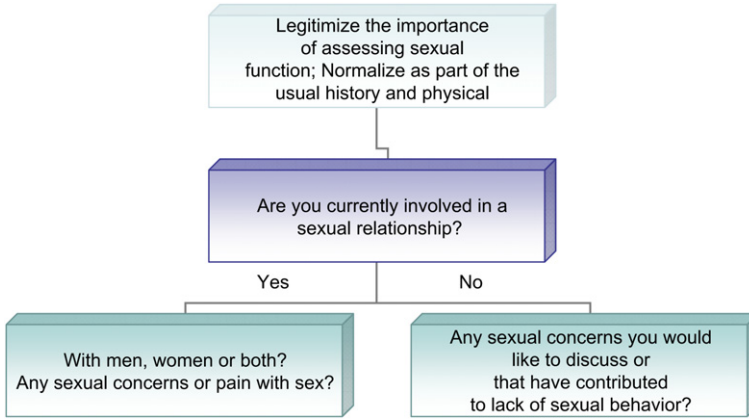

Fig. 1. Basic screening for sexual function.

a physician assumes that a 65-year-old widow may only seek out sexual relationships with men, she is denied the opportunity to discuss any other behavior to the contrary. In addition, even if partners' genders are not immediately relevant, the message that the physician does not hold preconceived notions may give patients the courage to discuss a sexual concern at a later time.

It is always helpful to start from a woman's current reproductive stage or presenting issue and then move on to her sexual function, saying, for example, ''Menopausal women (or women who have recently had a baby) often notice problems with decreased lubrication, discomfort with sexual intercourse, or decreased sexual desire. Have you noticed any changes?''

If a sexual complaint is identified during the basic screening, it should be determined whether (1) the concern can be addressed during the current appointment, (2) a follow-up visit is needed that is specifically focused on addressing the concern, or (3) the sexual concern or complaint is beyond the scope of training or comfort of the physician and the patient should be referred to a specialist. It is always important to legitimize the problem for the patient and to attend to patient discomfort and defer sensitive questions for a later time or supply alternative responses for patients if they seem too embarrassed to provide explicit sexual details [19].

Elements of a complete sexual history. A thorough sexual history should cover medical, reproductive, surgical, psychiatric, social, and sexual information [19–21]. Sexual functioning is multifactorial and therefore each domain of function must be assessed as to its individual or combined impact.

In the not-so-distant past, most sexual dysfunctions were believed to be primarily psychologically based. Ironically, some feminists, in an attempt to argue that the field of medicine is pathologizing normal female sexuality, continue to deny a biologic component to female sexual problems. Given

the multifactorial nature of the sexual response, however, it is obvious that biologic factors may contribute to the cause or maintenance of sexual problems and must be considered.

If not already completed as part of the routine history and physical examination, the relevant medical information for a thorough sexual assessment includes:

- past medical history
- current health status
- reproductive history and current status (age at menarche, menstrual history, pregnancies, losses, and consequences of deliveries [eg, episiotomies], infertility, birth control and contraception, sexually transmitted illnesses, gynecologic pain, surgeries, urinary system)
- endocrine system (eg, diabetes can impair arousal and orgasm, androgen insufficiency has been linked to hypoactive desire, estrogen deficiency has been linked to vaginal atrophy and arousal problems, thyroid conditions can impair sexual desire)

Box 3. Some medications known to have sexual side effects

Psychotropic medications
Antidepressants (SSRIs, serotonin-norepinephrine reuptake inhibitors [SNRAs], tricyclic anti-depressants, monoamine oxidase inhibitors [MAOIs])
Antipsychotics
Benzodiazepines
Mood stabilizers

Antihypertensives
Beta-blockers
Alpha-blockers
Diuretics

Cardiovascular agents
Lipid-lowering agents
Digoxin

Histamine H2-receptor blockers

Hormones
Oral contraceptives, estrogens, progestins, antiandrogens, GnRH agonists
Narcotics
Amphetamines
Anticonvulsants
Steroids

- neurologic diseases (eg, multiple sclerosis and spinal cord injuries can impair arousal and orgasm)
- cardiovascular disease (has been linked to arousal disorder) [22]
- psychiatric illness (eg, depression can impair desire, as can medications to treat psychiatric conditions, such as SSRIs).

Current use of prescription and over-the-counter (OTC) medicines should be elicited because of the potential sexual side effects that many have. Patients are not likely to spontaneously report the use of OTCs, and physicians need to inquire directly to elicit this information. Box 3 lists some commonly prescribed medications associated with sexual side effects [17,23–25].

A patient's history may not be sufficient to assess her sexual function, and a physical examination or laboratory testing may help in determining the physiologic factors involved in a sexual complaint. Table 1 lists the elements to be included specifically in a gynecologic physical examination and related conditions that may cause sexual problems.

In addition, the examination should include evaluation of blood pressure, heart rate, peripheral pulses, edema, and a neurologic screen to assess sensation [20,23].

Table 1
Elements of a gynecologic examination and conditions that may impair sexual function

Examination	Condition to consider
Inspection of external genitalia	
Muscle tone, skin color/texture, skin turgor and thickness, pubic hair amount, vaginal pH	Vaginismus, vulvar atrophy, vulvar dystrophy
Cotton swab test of vulva, vestibule, hymenal ring, Bartholin and Skene glands (pain mapping)	Vulvar vestibulitis
Expose clitoris	Adhesions
Examine posterior forchette and hymenal ring	Episiotomy scars, strictures
Monomanual examination	
Palpate rectovaginal surface, levator muscles, bladder/urethra	Rectal disease, vaginismus, levator ani myalgia, interstitial cystitis, urinary tract infection
Evaluate vaginal depth	Postoperative or postradiation changes, stricture
Bimanual examination	
Palpate uterus and adnexa and perform rectovaginal examination	Fibroids, endometriosis, masses, cysts
Speculum examination and papanicolaou smear	Atrophy, human papilloma virus infection, cancer, cystocele, rectocele, uterine prolapse

Adapted from Phillips NA. The clinical evaluation of dyspareunia. Int J Impot Res 1998;(suppl 2):S117–20.

Suggested laboratory studies include a hormonal profile, fasting glucose, thyroid function, liver function, and cholesterol and lipid levels [20,23]. Androgen levels should be measured when they are at their highest, on days 8 to 10 of the menstrual cycle.

Elements of a complete sexual assessment. Box 4 [26] lists questions that help identify the essential components of a sexual complaint. These questions are designed to elicit the patient's perceptions of the problem, timeline, context (the quality of the relationship, other stressors), and current health problems that might be affecting sexual function. These questions are also designed to elicit which components of the sexual response (desire, arousal, orgasm) or pain are compromised. This information assists the physician in diagnosing the primary (and secondary, if present) dysfunctions and provides important data to help determine etiology and even the basis for treatment considerations (eg, education, psychotherapy, medication).

Box 4. Essential questions to include in a sexual assessment

How does the patient see or describe the problem?
How long has the problem been present? (Also specify if life-long or occurred after a period of normal function)
Was the onset sudden or gradual?
Is the problem specific to a situation or partner or is it generalized?
Were there likely precipitating events (biologic or situational)?
Are there problems in the patient's primary sexual relationship (or any relationship in which the sexual problem is occurring)?
Are there current life stressors that might be contributing to sexual problems, and if so, how is stress perceived and managed?
Is there some underlying guilt, depression, or anger that is not being directly acknowledged?
Are there physical problems, such as pain?
Are there problems with desire, arousal, or orgasm, and can the patient determine the primary problem?
Is there a history of physical, emotional, or sexual abuse that may be contributing?
Does the partner have any sexual problems?

Data from Basson R. Eliciting the sexual concerns of your patient in primary care. Available at: www.medicalsexuality.org/November 2000. Accessed October 17, 2006.

Scales, questionnaires, and checklists

Although a face-to-face interview is ideal, particularly when addressing a potentially sensitive topic, paper-and-pencil questionnaires can be valuable. Waiting room questionnaires allow for a quick and easy initial screening of sexual function, and responses can be discussed during the consultation. Moreover, patients learn early in the office visit that sexual health is of importance to the physician and is appropriate to discuss. The information on the questionnaire provides useful information to help direct the physician to particular problem areas. Box 5 displays the Brief Sexual Symptom Checklist, a short and easy screening tool that can be incorporated into a patient intake form [27]. Some patients may not feel comfortable completing the form, however, and may need or prefer more direct questioning from the physician. In addition, Meston [27] has developed a slide kit that describes the most commonly used and well-validated sexual function assessment tools (see Box 6). This kit is available online at http://www.femalesexualdysfunction.org, a website on female sexual dysfunction that is sponsored by Baylor College of Medicine. Meston presents the validity and reliability of the assessment tools

Box 5. Brief Sexual Symptom Checklist

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

1. Are you satisfied with your sexual function?
   ☐ Yes ☐ No
   If No, please continue.
2. How long have you been dissatisfied with your sexual function?
   _____

3a. The problem (8) with your sexual function is: (mark one or more)
   1. Problems with little or no interest in sex
   2. Problems with decreased genital sensation (feeling)
   3. Problems with decreased vaginal lubrication (dryness)
   4. Problems reaching orgasm
   5. Problems with pain during sex
   6. Other:

3b. Which problem is most bothersome *(circle)* 1 2 3 4 5 6 7

4. Would you like to talk about it with your doctor?
   ☐ Yes ☐ No

From Hatzichristou D, Rosen RC, Broderick G, et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. J Sex Med 2004; 1:57; with permission.

Box 6. Female Sexual Function Scales available from www.femalesexualdysfunctiononline.org

Brief Index of Sexual Functioning for Women (BISF-W)
Changes in Sexual Functioning Questionnaire (CSFQ)
Derogatis Interview for Sexual Functioning (DISF/DISF-SR)
Female Sexual Function Index (FSFI)
Golombok-Rust Inventory of Sexual Satisfaction (GRISS)
McCoy Female Sexuality Questionnaire (MFSQ)
Sexual Interest and Desire Inventory–Female (SIDI-F)
Sexual Quality of Life–Female (SQOL-F)
Hypoactive Sexual Desire Disorder Screener (HSDD Screener)

and their recommended uses and provides information about how to obtain the tools from investigators or distributors.

Referrals

The decision of whether to refer a patient who has sexual dysfunction depends on the physician's comfort and level of expertise and the complexity of the dysfunction [18]. In addition, some sexual problems are best treated by specialists (eg, sex therapist, marital therapist) or by a multidisciplinary approach.

If a referral is made, however, it is important for patients to recognize this as good health care. Patients also need some reassurance that a referral is not a cloaked attempt to get rid of the patient, which leaves her feeling rejected or feeling that her physician thinks the problem is "all in my head."

Summary

Why should you inquire about sexual concerns?

The importance of sexual health to a woman's quality of life and general health and well-being cannot be overstated, yet the topic is too often ignored by gynecologists and primary care physicians. This article has been geared toward helping overcome some of the barriers to physicians simply opening the door to the topic and conducting at least a basic sexual history and screening of sexual concerns. Although treatment options are addressed elsewhere in this issue, the most effective treatment of all is to *ask*. You cannot treat a problem if you do not know it exists.

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Disorders of Sexual Desire and Arousal

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Disorders of sexual desire are the most common sexual problems reported by women. Surveys from various countries find that 10% to 51% of women report decreased sexual desire. A low level of desire is often associated with difficulty in arousal and orgasm as well as with sexual dissatisfaction.

Decreased sexual desire is one of the most common problems seen in a primary care or OB/GYN office. However, many physicians receive little or no training in sexual problems and thus do not know how to diagnose and treat the condition. As a result, the condition is often undiagnosed and untreated despite its common occurrence.

A variety of terms have been used to describe disorders of sexual desire and arousal, including: sexual avoidance, low libido, inhibited sexual desire, hypoactive sexual desire, hypoactive sexual desire disorder (HSDD), female sexual arousal disorder, and sexual aversion disorder. There is no consensus on the definitions of these terms, and many authors and investigators have struggled to define the syndromes that they see. There is not a universally accepted tool to define the various disorders, and some patients seem to have components of more than one diagnosis. This article presents three models of sexual desire in women, an approach to differential diagnosis, and some methods that can be used by a practicing physician.

Epidemiology and risk factors

Prevalence

It is difficult to estimate the prevalence of desire disorders. Laumann and colleagues [1] reported on a national probability sample of 1749 women aged 18 to 59 years. Of these, 43% reported a sexual dysfunction. Among the 2400 midlife multiethnic women (Hispanic, white non-Hispanic, African

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American, Chinese, and Japanese) in six United States cities who completed baseline questionnaires in the prospective Study of Women's Health across the Nation, 40% reported that they never or infrequently felt sexual desire [2]. Addis and colleagues [3] surveyed 2109 women aged 40 to 69 years who were randomly selected from longterm Kaiser–Permanente members. Of these, 6.6% reported that lack of interest was "very much a problem," and another 16.6% reported it to be "somewhat of a problem."

These reports were based on written surveys. Most ask a few questions about sexual desire, often incorporated into other questions about sexual satisfaction. It may be difficult to distinguish desire disorders from other sexual dysfunctions, as well as hypoactive desire disorder from sexual aversion in surveys. Although the exact prevalence of desire disorders may be difficult to determine, it is clear that they are common.

Risk factors

Sexual desire is an appetite and is closely related to reproduction. It is governed by a complex set of inhibitory and excitatory influences. Clinicians have long recognized that disorders of desire may be related to other sexual dysfunctions, including sexual arousal disorder, dyspareunia, and orgasmic disorder. Sexual desire is profoundly influenced by emotion. Anger, fear, and anxiety inhibit sexual desire. Relationship issues, prior sexual experiences, and overall mental and physical health may profoundly impact sexual desire.

Several investigators have reported on associations between sexual desire disorders and other risk factors. Most used survey data. Relationship factors, attitudes toward aging, and poor mental or physical health are consistently found to be associated with decreased desire [1–16]. Women who experienced multiple childhood sexual abuse are more likely to have decreased desire than those who had a single incident or no abuse [17,18]. Decreased sexual desire is associated with increasing age [12,14], menopause [10], surgical menopause compared with natural menopause [11], parity [19], and other sexual problems [6]. Several investigators have found that sexual desire is related to race or ethnicity, with black women reporting fewer problems than white or Asian [2,3].

Chronic illnesses may be associated with decreased sexual desire. Hypothalamic/pituitary disorders are associated with sexual dysfunctions in men and women [20]. Women who have type I diabetes were more likely than controls to report problems with arousal and lubrication [7]. Adrenal insufficiency is associated with decreased desire and arousal [21]. Chronic renal failure is associated with decreased desire in women [22]. Patients who have multiple sclerosis report decreased desire and other dysfunctions [23–25]. Depression is strongly associated with decreased desire [26–28]. Hyperprolactinemia has been associated with sexual dysfunctions including decreased desire [29].

The relationship between hormone levels and sexual desire is not clear. Several investigators have attempted to correlate hormone levels with sexual function. Estradiol levels are correlated with vaginal dryness, dyspareunia, and sexual behavior [30,31]. Other hormone levels have not been consistently associated with sexual function [32]. Serum androgen levels correlate poorly with sexual function in women in most studies. Dennerstein and colleagues [31] failed to find an association between testosterone levels and sexual function in a cohort of 201 women, and again [33] in a cohort of 438 women aged 45 to 55 years. Davis and colleagues [34] studied 1021 women aged 18 to 75 years that were randomly selected from Australian voter rolls. No relationship was found between any measure of sexual function and serum testosterone or androstenedione levels. A low domain score for sexual responsiveness for women aged 45 years or older was associated with higher odds of having a serum dehydroepiandrosterone sulfate level below the 10th percentile, and in women aged 18 to 44 having a low domain score. However, they found that no single androgen level was predictive of low female sexual function, and most women with low dehydroepiandrosterone sulfate levels did not have low sexual function.

Kirchengast and colleagues [35] found that body build was related to decreased sexual desire in postmenopausal women, but found no relationship between androgen levels and sexual desire. Bancroft and colleagues [36] found that oral contraceptives decreased serum androgens, but that there was no relationship between androgen levels and sexual desire.

Several investigators have attempted to determine differences in androgen levels between women with low desire and control groups. Bancroft and colleagues [37] compared women with low desire on oral contraceptives to controls on oral contraceptives. No differences in androgen levels were found between the two groups. Schreiner-Engel and colleagues [38] found no differences between testosterone, free testosterone, or prolactin levels between women with low desire and controls.

There may be some associations between some hormone levels and sexual desire, however, it is clear that general mental health, prior sexual experience, childhood sexual abuse, and relationship issues are more significant than hormonal status as risk factors for decreased sexual desire.

Models of sexual desire in women

Masters and Johnson

Masters and Johnson advanced our knowledge of human sexuality. Masters was the first to describe a physiologic model for the sexual response cycle. His original model did not include a desire phase because he did not consider desire disorders to be sexual dysfunctions; he used the term *dysfunction* to describe "an altered state of physiologic responsivity." Rather,

he considered inhibited sexual desire and sexual aversion to be nondysfunctional diagnostic categories.

Biphasic model

Masters separated sexual arousal from orgasm, and was the first to differentiate different sexual dysfunctions. The original model described by Masters and Johnson described the well-known phases of excitement, plateau, orgasm, and resolution (Fig. 1). This model can be thought of as a biphasic model of excitement and orgasm, with plateau being a state of excitement and resolution being an absence of excitement.

One of Masters' concepts is that sex is a natural function, and that the appetite for sex is a natural and innate desire. Masters believed that there were few if any people who had never felt sexual desire [39]. Sexual desire cannot be taught, but can be inhibited or augmented. Sex therapy is a learning process. The approach to desire phase disorders was to identify "blocks" to desire and learn the way to avoid these blocks. Masters approached desire phase disorders with sensate focus exercises and "I" language. In "I" language, couples are instructed to use structured sentences that begin with "I feel." The sentences should express an emotion, not a thought. The emotion is a reaction that is not under voluntary control. For example, a statement like, "I feel like you put work over our relationship," is a thought. A statement like, "I feel rejected and hurt when we don't have intercourse," expresses an emotion.

Masters believed that sexual activity occurred in a relationship, and that sexual dysfunctions occurred in a relationship. One of his concepts was that the relationship was the patient, and therefore successful treatment depended on treating the relationship. Each partner contributes to the relationship, and the patient can only change his or her contributions.

Masters also believed a person engaged in sex for their own pleasure and enjoyment. One key to successful therapy was for the patient to learn to engage in sex for his or her own interest. Because sexual response is a natural function under involuntary control, the same stimuli will not always give the same response. Patients must learn to recognize the response that they are having currently rather than the one they may have had in the past.

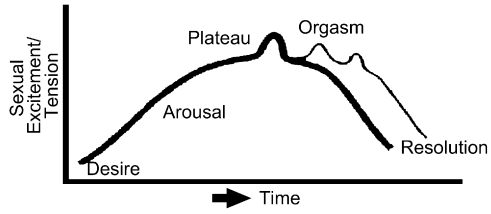

Fig. 1. Masters and Johnson/Kaplan model of sexual response. (*Adapted from* Masters WH, Johnson VE. Human sexual response. Boston: Little Brown and Co.; 1996.)

Helen Singer Kaplan

Kaplan greatly increased our understanding of desire phase disorders. In her landmark book, *Disorders of Sexual Desire*, she outlined the "triphasic" model of sexual response – desire, excitement, and orgasm. She distinguished hypoactive sexual desire from inhibited sexual desire. Kaplan stated, "On one level, the sexual dysfunctions, as well as the sexual phobias, are caused by a single factor—anxiety" [40]. Anxiety interrupts the sexual response cycle. Disorders of the desire phase occur when anxiety occurs early in the cycle, during the desire phase. The first stirrings of sexual desire induce anxiety, which suppresses sexual desire. Kaplan believed that the involuntary and unconscious but active suppression of sexual desire is the immediate cause of inhibited sexual desire. Patients suppress desire by implementing "turnoff" mechanisms of negative thoughts. These thoughts have no specificity, and may include: unattractive physical features of the partner, prior unacceptable behavior of the partner, negative thoughts about themselves, or nonerotic distractions such as concerns about work, homemaking, children, or other concerns. Fear of performance or failure can also act as a turnoff.

Patients may invoke unconscious defenses as part of a turnoff. They are not aware of their role in the turnoff and often see themselves as victims. They externalize: "I have no interest in him because he is a slob, old, fat, and unclean." They report that they "don't feel anything" in a sexual situation and feel relief if sex is avoided. Patients are generally not aware that they really do not want to have sex. They may develop avoidance behaviors such as staying up until their partner is asleep, going to sleep before the partner is in bed, wearing bedclothes that make intercourse impossible, watching television, reading, or using the computer until their partner is asleep.

Kaplan believed that anger toward the partner is a common cause of loss of sexual interest. All couples will be angry at eachother at some time. Chronic anger can have its origin in infantile transferences: she is angry because husband/daddy neglects her for business or controls her or threatens her with abandonment; he is angry because she does not give him what he needs/wants, or prefers others such as brothers, fathers, or children. The spouse of a patient with inhibited desire will be sexually rejected and will be hurt and angry. The anger over the sexual rejection can feed back into an anger cycle related to infantile transference, so both partners feel victimized and hurt.

Rosemary Basson

Rosemary Basson has described another model of sexual desire in women (Fig. 2) [41]. Basson believes women have many motivations and reasons for engaging in sex. Sexual desire may be an infrequent reason for engaging in sex in an established relationship. The desire for emotional closeness and intimacy is a primary force for women to seek out sexual activity,

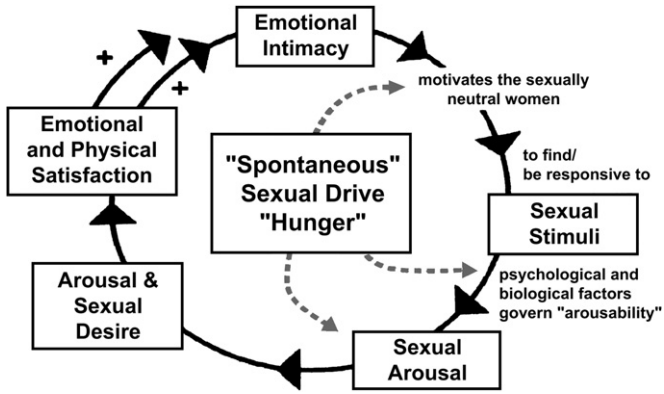

Fig. 2. Basson's model of female sexual arousal and desire. (*From* Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 2001;98:350–3; with permission.)

particularly in an ongoing relationship. The desire for emotional intimacy motivates the sexually neutral women to be responsive to or seek out sexual stimuli. Psychologic and biologic factors govern arousability. The sexual stimuli lead to arousal, which further augments arousal and desire. Culmination of this leads to the emotional and physical satisfaction and experience of emotional intimacy. Satisfactory completion of the cycle motivates the woman to seek out this experience in the future.

According to this model, female sexual desire is motivated by several factors in addition to the potentially powerful biologic drive. The desire to become aroused may be motivated by the desire to share emotional closeness and expression of affection. The desire for adventure, rebellion, or to conceive a pregnancy may augment the sexual response cycle. The amount of the contribution of each may vary. The biologic drive may be heightened by a period of abstinence, a new relationship, periovulatory, or erotic stimuli (auditory, visual, olfactory, tactile, mental) that may prompt the woman to seek out or respond to sexual stimuli.

In the absence of proper activation of this response cycle, sexual touch, words, or actions may be experienced as unwanted or offensive. Sexual stimuli may inhibit the cycle when a woman is not in a responsive state. Emotional issues such as prior molestation, which may activate negative memories, may completely shut down the cycle. A dysfunctional partner or emotionally distant relationship may reduce the desire for intimacy with that partner. Past or present emotional or physical abuse may likewise engage negative emotions when the sexual response cycle is activated, leading to its inhibition or shut-down. Painful intercourse, poor technique, inadequate duration of stimulation, or frequent inability to achieve a desired orgasm may inhibit a woman's willingness to allow activation of the response cycle. Depression may leave a woman emotionally unavailable for intimacy.

Each of these models is useful in understanding female sexual desire and arousal. Female sexual behavior, arousal, and desire are complicated and are not completely understood. The sexual response cycle is a continuum, with one phase blending into another without sharp distinctions. Sexual dysfunctions likewise exist in a continuum, and an individual patient may have elements of hypoactive desire disorder, sexual aversion, and excitement disorder.

Differential diagnosis

Hypoactive desire disorder, sexual aversion, and female sexual arousal disorder

Patients often present with the complaint, "I just don't have any interest in sex." Successful therapy for these patients depends on an accurate diagnosis. Unfortunately, there is no consensus on diagnostic definitions. The *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (Text Revision) definitions of desire and arousal disorders are shown in Box 1. The international multidisciplinary group gathered by the American Foundation for Urologic Disease definitions are shown in Box 2. Although these definitions are similar, they differ in some respects.

The definitions may not be helpful in assigning a diagnosis. Furthermore, it is not at all clear that the syndromes described are truly distinct. Many patients who complain of hypoactive sexual desire also have components of aversion, but may not have a phobic avoidance. There is often considerable overlap between arousal disorders and decreased desire. An individual patient may have elements of sexual aversion, HSDD, and arousal disorder that may manifest differently at different times.

Arousal and desire disorders can only be distinguished by history. I find it useful to describe a model of sexual response to a patient and then ask them, "What happens to you?" Patients who have sexual aversion often describe avoidance behaviors. They may stay awake until their partner is asleep, go to bed and sleep or feign sleep before their partner comes to bed, or read or work on the computer until their partner falls asleep. They often describe a sensation of anxiety, dread, or fear when they are in a situation in which their partner makes or might make a sexual advance. For example, patients may describe a feeling of anxiety if their partner suggests dinner out, because "I know he will want to have sex when we get home."

Patients who have sexual aversion may be able to perform at times, and may have normal excitement and orgasm. Just as someone may be able to overcome a fear of flying to make an important trip, a patient with sexual aversion may be able to have intercourse to please their partner, out of a sense of obligation, or because a desire for intimacy or romance overrides the fear of intercourse. Patients with sexual aversion may masturbate to orgasm without difficulty [42].

Box 1. *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* definitions of desire and arousal disorders

Hypoactive sexual desire disorder

Diagnostic criteria for 302.71 hypoactive sexual desire disorder

A. Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and the context of the person's life.
B. The disturbance causes marked distress or interpersonal difficulty.
C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

Female sexual arousal disorder

Diagnostic criteria for 302.72 female sexual arousal disorder

A. Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement.
B. The disturbance causes marked distress or interpersonal difficulty.
C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

Sexual aversion disorder

Diagnostic criteria for 302.79 sexual aversion disorder

A. Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner.
B. The disturbance causes marked distress or interpersonal difficulty.
C. The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction).

From American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, text revision. Washington, DC: American Psychiatric Association; 2000; with permission.

Box 2. American Foundation for Urologic Disease definitions of female arousal and desire disorders

Hypoactive sexual desire disorder: chronic lack of interest in sexual activity
Sexual aversion disorder: persistent or recurrent phobic avoidance of sexual contact with a partner
Sexual arousal disorder: persistent or recurrent inability to attain or maintain sexual excitement

These disorders must cause the woman distress in order to qualify as a female sexual dysfunction.

Adapted from Basson R, Berman J, Burnett A, et al. Report of the International Consensus Development Conference on Female Sexual Dysfunction: definitions and classifications. J Urol 2000;163:888–93.

HSDD is a deficiency or absence of sexual fantasies and desire for sexual activity. The condition causes distress to the patient. The patient never or rarely initiates sexual activity and is not receptive to sexual advances. The condition may be primary or secondary, and general or specific to a certain partner. Patients who have HSDD do not have an aversive reaction to a sexual advance. Acquired HSDD may result from boredom or unhappiness in established relationships. Fatigue and stress can contribute to the disorder. Anxiety about sex is always present to some degree.

Patients who have HSDD may suffer from poor self-esteem or body image. A person who considers herself unattractive may have a low desire for intercourse. Fear of failure, fear of loss of control, power issues in a relationship, and early negative conditioning about sex are common issues in patients who have HSDD.

Arousal disorders are characterized by failure of excitement and are often caused by anxiety or pain. Patients describe inability to lubricate, difficulty with penetration, or pain with penetration. They may have normal desire or may develop inhibited desire. Vasoactive drugs can inhibit arousal.

Other sexual dysfunctions

Disorders of sexual desire may be secondary to another sexual dysfunction such as dyspareunia or orgasmic dysfunction [43]. Patients who have dyspareunia, such as vulvar or vaginal disease, or endometriosis often develop HSDD or arousal disorder. Pain is both a potent inhibitor of the sexual response cycle and a potent modifier of behavior. Arousal disorder and orgasmic disorder may lead to inhibited desire.

Marital discord is associated with decreased desire [16]. Patients with inhibited desire report lower levels of intimacy [44].

Male sexual dysfunctions

Female partners of men who have erectile dysfunction may experience decreased desire. These men may avoid sexual encounters, which may be interpreted as rejection by their partners. The female partners may be anxious about their partner's performance, leading to decreased desire. Treatment of erectile dysfunction can improve desire and arousal in female partners [45].

Domestic violence

Women who are in a violent relationship have high rates of sexual dysfunction including desire disorders. Chapman [46] found that 61% of women who suffered from domestic violence had sexual dysfunctions. Schei and Bakketeig [47] found an association between sexual problems and domestic violence as well. All women who present with complaints of decreased desire should be screened for domestic violence.

Depression

Depression is strongly associated with decreased desire [27,48]. The relationships between depression, marital distress, and sexual dysfunction are complex. The relationships between sexual dysfunctions, depression and antidepressants are discussed in detail elsewhere in this issue. Women who present with complaints of decreased desire should be screened for depression.

Substance abuse

Substance abuse is associated with decreased desire. Abuse of alcohol, narcotics, marijuana, and cocaine has been associated with decreased desire. The associations of substance abuse and sexual dysfunctions are discussed in detail elsewhere in this issue. A patient who presents with decreased desire should be screened for substance abuse.

Androgen deficiency

Androgen deficiency is covered in detail elsewhere in this issue.

Approach to the patient

History

A complaint of decreased desire may be overt or may be uncovered in a review of systems. A complete sexual history is described elsewhere in this issue. A general medical history should be taken, with emphasis on uncovering chronic illness such as those described above. A menstrual history may uncover thyroid disorders or hyperprolactinemia. A complete

list of medications including over-the-counter and herbal preparations should be obtained. The patient should be screened for domestic violence, relationship issues, depression, and substance abuse.

In a patient who has decreased desire, the history should be directed to the differential diagnosis. It is important to determine if there is any history of sexual abuse or assault. It should be determined if the condition is primary or secondary, and if it is general or specific to their partner.

How often does intercourse occur? Does the patient masturbate? Patients with sexual aversion may masturbate to orgasm without difficulty. Most patients with decreased desire report decreased frequency of intercourse, but some patients may have frequent intercourse because they feel pressured or forced. These patients often resent having intercourse when they do not want to, leading to anxiety or anger and further inhibition of desire. Patients who have infrequent intercourse may feel guilty because they know their partner is frustrated, leading to anxiety and inhibition of desire.

It is essential to determine what happens to the patient when a sexual advance is made. What does the patient feel? Is there anxiety, fear, or dread? When else has the patient felt like that? Patients may describe a feeling of anxiety that relates to prior experiences. Exploring when the patient also felt that way can lead to episodes of prior sexual abuse. There may be unresolved conflicts in a relationship related to power struggles. The patient may relate that they feel the same way about intercourse that they feel about financial conflicts or other decisions that the couple must make.

How does the patient know if their partner is making a sexual advance? Who initiates sexual activity? Most sexual advances are nonverbal, and the rejection of advance is also nonverbal. Paradoxically, some patients who have desire disorder are always the ones who make a sexual advance that ends in intercourse. Their partner may have been conditioned by frequent rejection to rarely make advances.

Does the patient have poor self-image? Patients may reveal that when they are in a sexual situation, all they can think about is that their thighs are too fat or breasts are too small or some other negative self-image.

Are there avoidance behaviors? Does the patient avoid situations where intercourse might occur? Common avoidance behaviors include reading or working on the computer until their partner is asleep, or caring for children until the partner is unavailable. Patients with sexual aversion may have a variety of ''reasons'' to avoid sex. These include: the children might hear, someone might see in the window, the room is too cold, they are too tired. They may also project reasons onto their partner (eg, he is too fat or undesirable for some reason).

Does the patient ever have sexual thoughts or dreams? Do they read romance novels, watch romantic movies, or romantic television shows? Do they have fantasies about an actor or someone else? Patients who have sexual aversion often sublimate their desires. They may state that they never have sexual feelings or desires, but when asked about romantic novels or movies express

that they have a desire for romance. As the desire for romance or love is explored, the patient may express a desire for intercourse, but initially denies it as a sexual feeling. Patients often deny their contribution to the sexual dynamic.

Is there marital distress? Patients often will initially deny that there is any conflict in the relationship. Often they will state, "he really understands" or "he is just so patient." However, further exploration often uncovers marital problems. Ask the patient if they ever fight. A couple that never has any disagreements is often so detached emotionally that they cannot interact for fear of losing the relationship. Are there financial problems in the relationship? Sex and money are surrogates for power and control. Patients may be angry over control issues and use sex and money to exert control. Do both partners have a career? Are there issues over child rearing? A patient who "gave up" his or her career or feels that he or she is required to have both a career and be responsible for childcare or housework may be angry, leading to decreased desire.

Does the patient suspect their partner of infidelity? Partners whose sexual advances are rejected may seek other outlets. The patient who has decreased desire may then have feelings of betrayal and anger that further inhibit desire.

Partner rejection may be an important cause of decreased desire. The patient may be in a relationship that they want to end, but cannot because of religious conviction, financial dependence, or family pressures. The patient may suppress sexual desire because they reject their partner.

Is there another sexual dysfunction? Pain is a potent modifier of behavior. Patients who experience emotional or physical pain with intercourse may become conditioned to avoid it. Is there a male sexual dysfunction? Patients may interpret erectile dysfunction as a rejection. Premature ejaculation can lead to impaired orgasm on the part of the female, and lead to frustration and subsequent inhibition of desire.

Physical

The physical examination should include signs of androgen insufficiency, estrogen deficiency, or galactorrhea. The pelvic exam should include a careful inspection for vulvar dystrophies or vaginitis. Pain on bimanual examination may suggest intra-abdominal pathology.

Laboratory evaluation

Thyroid tests and prolactin levels may be indicated if there is any suggestion of hyperprolactinemia. Androgen levels are not useful in the majority of cases.

Therapeutic approaches

Therapy for desire phase disorders is difficult. There is minimal data on the effectiveness of different therapeutic approaches [49]. Masters and Johnson reported a success rate of over 90% for sexual aversion using sensate focus

therapy [39]. They reported that low libido required an intensive psychotherapeutic approach. Kaplan stated that only a small proportion of patients who have inhibited sexual desire responded to brief sex therapy. Therapy must be directed toward the etiology of the dysfunction. Therapy is guided by history and must be individualized. We must be careful not to "medicalize" desire disorders nor overlook the contribution of medical problems to decreased desire.

There is no standard definition for successful therapy. Increased frequency of intercourse can be measured but may not reflect success. Increased satisfaction with sex or marriage is subjective and difficult to verify. As a result, it is difficult to compare therapeutic regimens.

Counseling

Cognitive behavioral therapy

Cognitive behavioral therapy focuses on the role of thinking in how we feel and act. The theory is that thinking causes patients to feel and act the way they do. Therapy is directed to replacing negative thoughts with thoughts that lead to more desirable feelings and behaviors. In this paradigm, decreased sexual desire is caused by negative thoughts about sex or the partner. Replacing these thoughts with positive ones leads to a change in behavior and feelings. Trudel and colleagues [50] reported that combination cognitive behavioral therapy and sex therapy was successful in improving sex and marital satisfaction in 74% of women.

Brief interventional therapy

Brief interventional therapy may be successful in patients who have superficial anxiety issues or boredom. Resolution of a superficial problem such as boredom may be addressed by education or specific suggestions for change in behavior.

Marital therapy

Patients who have significant marital distress need marital therapy as part of treatment for decreased desire. Issues related to partner rejection or power and control must be resolved for therapy to be successful.

Intensive sex therapy

Intensive sex therapy involves sensate focus exercises as an educational tool. Intensive sex therapy has been reported to be effective in sexual aversion and arousal disorders, but less so in HSDD.

Pharmacologic therapy

A variety of pharmacologic approaches have been advocated. The US Food and Drug Administration has not approved any drugs for treatment

of HSDD or female sexual arousal disorder. Prescription drugs and herbal and alternative therapies are discussed in detail elsewehere in this issue.

Summary

Desire and arousal disorders are very common. These disorders can cause significant distress to a patient. A successful approach depends on an accurate diagnosis, which is dependent on history. Laboratory evaluation is usually not helpful, whereas psychosexual therapy is helpful in many cases. Although there is some evidence that drug therapy is helpful in some cases, no drug has been approved for the treatment of these disorders.

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Dyspareunia

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Dyspareunia, better termed women's sexual pain, is a heretofore poorly understood disorder once believed to be purely psychologic in etiology. Thanks to cooperative research efforts from several specialties aimed at defining subsets of the disorder, our understanding the etiology of subsets and their comorbidities and new concepts for diagnosis and management are being validated or are being put into practice. This article describes the surprising prevalence of sexual pain, outlines new definitions for subtypes of sexual pain and diagnostic criteria for them, and applies these diagnoses to the task of selecting treatment options.

Prevalence

World prevalence of women's sexual pain has recently been summarized in a World Health Organization (WHO) sponsored meta-analysis of subtypes of chronic pelvic pain [1]. The prevalence of dyspareunia was found to be substantially higher in the United States (45%) than in northern European developed nations such as Sweden, where the prevalence is 1.8%. When only the highest quality studies were analyzed, the rates were found to range from 8% to 21.8%. Though there were few studies from developing countries, their prevalence rates were generally lower. The WHO study is notable because search criteria were applied to dysmenorrhea and noncyclic pelvic pain in addition to dyspareunia, thus placing data on sexual pain in a recognizable context. This information is important to policy makers determining health care expenditures, but perhaps even more important to practitioners, because it indicates a need to ask specific questions about sexual discomfort at routine visits.

Prevalence of sexual pain should also be viewed in the context of sexual difficulty and dysfunction. In this context, Hays and coworkers have

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recently reviewed published prevalence studies that only reported all four categories of sexual difficulty—disorders of desire, arousal, orgasm, and pain [2]. They were careful to exclude studies that did not consider all four difficulties, that were based on convenience sampling, or that had response rates less than 50%. They found that among women who had *any* sexual difficulty, 26% (range, 7%–58%) experienced sexual pain, whereas 64% experienced desire difficulty, 31% experienced arousal difficulty, and 35% experienced difficulty with orgasm. Though the investigators could not test for potential interaction between categories, it seems clear that many women with desire difficulty do not experience pain. This and similar concepts have led researchers to question whether sexual pain should be considered a sexual disorder or a pain disorder [3].

Characteristics and definitions of sexual pain

Patients presenting with sexual pain often report that their pain is perceived in a specific location or with a specific activity. For example, a patient may report a tearing or burning pain at the introitus that occurs with any attempted entry or that she ''clamps down'' because of pain, or she may report a deeper sensation that a painful structure is being contacted during deep penetration. Definitions correspond fairly well to these reports. Sexual pain can be broadly divided into dyspareunia and vaginismus, though there is clearly a large degree of overlap, because women who have vaginismus experience pain, and women who experience pain learn to avoid painful stimuli by contracting pelvic musculature. Dyspareunia, from the Greek *bed partners not fitting together*, is defined as recurrent or persistent pain associated with attempted or complete vaginal entry or penile vaginal intercourse [4]. For diagnostic and treatment purposes dyspareunia can be further subdivided into superficial (introital) pain and deep pain. Deep pain from endometriosis, adhesive disease, chronic cervicitis, leiomyomata, or other etiologies is usually distinct in presentation, pathology, and treatment. Superficial pain definitions overlap substantially with that of vulvar vestibulitis syndrome (VVS), defined by Friedrich as (1) severe pain with vestibular touch or attempted vaginal entry, (2) tenderness to cotton swab pressure localized to the vulvar vestibule, and (3) physical findings confined to various degrees of vestibular erythema. Of the criteria, pain with attempted entry and pain limited to the vestibule as confirmed by a cotton-swab test seem to be the most reliable diagnostic conditions [5]. VVS is a diagnosis of exclusion arrived at only when other causes of mucosal pain have been eliminated, whereas dyspareunia is a symptom.

In theory, vaginismus can exist without overt pain; however, in most cases it is accompanied by pain [6]. A revised definition of vaginismus was recently recommended by an international consensus committee: persistent or recurrent difficulties of the woman to allow vaginal entry of the penis, a finger, or any object, despite her expressed wish to do so [4]. There is

variable (phobic) avoidance and involuntary pelvic muscle contraction in anticipation or fear of the experience of pain [7].

Pathophysiology

The causes of women's sexual pain differ for each subtype with substantial overlap, particularly between superficial dyspareunia and vaginismus. Deep dyspareunia etiology generally can be thought of in differential diagnosis, much like noncyclic chronic pelvic pain with a localized presentation [8]. For example, although large leiomyoma of the fundus often cause a general pelvic pressure-like pain, a pedunculated posterior lower uterine segment fibroid that is undergoing red degeneration may cause exquisite deep dyspareunia. Similarly, just as endometriosis implants on the sigmoid colon can cause a shocking degree of pain during bowel movement, implants on the uterosacral ligaments can cause severe deep dyspareunia. Indeed, deep dyspareunia can result from any inflammatory process between the upper vagina and uterus. This pathophysiology is demonstrated by Nascu and colleagues' histologic evaluation and prospective follow-up of 27 premenopausal women who were found to have a normal pelvis at laparoscopy for chronic pelvic pain and dyspareunia [9]. All subjects underwent uterosacral ligament resection (LUNA) and histologic evaluation of the ligaments; pain was evaluated by questionnaire at 3, 6, and 12 months postsurgery. Endometriosis was found in 7%, endosalpingosis in 11%, and inflammation in 52% of specimens. Uterosacral ligament resection was associated with a significant ($P < .01$) decrease in deep dyspareunia and also in noncyclic pain. Nascu's conclusion regarding deep dyspareunia is supported by Juang and coworkers, who found a 67% short-term improvement and a 50% long-term improvement in deep dyspareunia [10]. Deep dyspareunia can also arise, following hysterectomy, in the vaginal cuff in 2.3% of women who were pain-free before surgery [11]. No pathologic mechanism for vaginal apex pain has been proposed to this author's knowledge.

The causes of superficial dyspareunia are less clear. The vast majority of women who have superficial dyspareunia localize their pain to the entrance of the vagina, in anatomic terms, the vulvar vestibule. Indeed, VVS is believed to be the most common form of superficial dyspareunia [12]. At one time it was universally accepted that, because the mucosa of the vestibule appeared normal, there was no organic disease and the pain was psychogenic. It has become clear that well-demonstrated morphologic, neurochemical, and functional alterations are present in the mucosa of patients who have VVS and underlie their *allodynia*, or perception of pain in response to a nonpainful stimulus [13]. For example, an increased number of intraepithelial free nerve endings have been reported [14], and neuropeptide content in these intraepithelial nerve endings demonstrates an immunoreactivity to calcitonin gene-related peptide (CGRP) characteristic of

increased sensitization [15]. More recently, the same investigators have used standardized quantitative sensory tests to demonstrate functional changes in the sensory nerve endings in the vestibular mucosa [13].

A pathway is emerging that suggests minor tissue injury, such as a subclinical vaginitis that doesn't easily resolve and leads to the production of local inflammatory mediators, causes a reduction in nociceptor threshold, leading to peripheral sensitization. These sensitized nociceptors later respond to weak, non-noxious stimuli with allodynia, and subsequent noxious stimuli result in an exaggerated pain response that exceeds the stimulus known as hyperalgesia. Allodynia and hyperalgesia can also arise by a process of central sensitization wherein non-nociceptive A-alpha and A-beta afferent signals are abnormally amplified in the central nervous system. The exaggerated pain may result from an increase in descending excitatory signals or decreased inhibitory signals (the cause of which is unclear) but in either case the result is increased sensitization of dorsal horn neurons. Central sensitization seems a reasonable explanation for common reports of pain exacerbation at times of increased stress [4].

What remains the most unclear is the cause of the initial sensitization. Evidence for inflammatory changes in several studies led investigators to postulate an infectious basis for VVS; however, attempts to confirm the presence of yeast or abnormal bacteria have been inconsistent at best [16]. *Candida* species have long been considered as potential contributors to VVS pathogenesis, but the concept has been difficult to substantiate because the rate of positive yeast culture in VVS is comparable to that in control subjects. Nonetheless, most patients have been treated multiple times with prescription or over-the-counter antifungal medications, often providing partial relief initially but diminishing benefit on subsequent flares [17]. Two research findings suggest an intriguing cause for sensitization. Bornstein and colleagues and Chaim and colleagues have demonstrated an increase in mast cells in vulvovaginal mucosa of patients who have vulvar vestibulitis in comparison to control subjects [18,19]. In a related finding, Regulez and colleagues reported that 100% of women who had vulvovaginal pain and negative fungal cultures had anti-*Candida* IgE antibodies in vaginal fluid, which are known to activate mast cell degranulation, whereas none of the women in the control group of asymptomatic *Candida* carriers was found to have IgE in vaginal fluid [20]. These and other clues that an allergic mechanism may underlie mucosal sensitization are tempered by the inability to improve symptoms by topical application of cromolyn cream [21]. It is likely that sensitization occurs early in the process, and pain is maintained by neuronal mechanisms.

Consideration of the role of psychologic factors in sexual pain requires one to distinguish dyspareunia without features of VVS from those with VVS, and from those with vaginismus [4]. Early conceptualization of VVS pain suggested a psychogenic cause, but recent studies do not support this theory [22]. Many studies, but clearly not all, report an increased prevalence

of anxiety and depression symptoms; in the balance it seems that these symptoms are a result of VVS, most likely associated with the fallout from living with the condition, rather than a cause. VVS patients were, however, remarkably able to respond to visual stimuli with arousal as measured by vaginal plethysmography, responding to explicitly depicted coitus stimulus to a greater degree than control subjects [23].

Those who have dyspareunia but who do not have documented VVS have been found to have increased rates of clinically relevant anxiety and depression disorders. The prevalence of these symptoms is supported by self-reported measurement of psychologic characteristics. Experiential and behavioral signs of psychotic symptoms and hostility are found more frequently, and women who have undifferentiated dyspareunia were found to be more erotophobic, to have an aversion to engaging in sex, and to have more difficulty experiencing sexual arousal [4,24]. These and other features seem to set undifferentiated dyspareunia apart, in psychopathology, from dyspareunia with VVS findings, and point to the need for more thorough psychiatric evaluation in the group without VVS findings, whereas the VVS dyspareunia group may benefit from stronger supportive efforts.

Psychologic characterization of patients who have vaginismus is hampered by the difficulty of distinguishing these patients from those who have other presentations of dyspareunia. For example, vaginal spasm and pain measures do not objectively differentiate between women who have vaginismus and those who have VVS [25]. When grouped subjectively, patients who had vaginismus demonstrated significantly higher vaginal and pelvic muscle tone and lower muscle strength and also displayed a significantly higher frequency of defensive or avoidant distress behaviors during pelvic examinations and recalled past attempts at intercourse with more affective distress. Vaginismus subjects were twice as likely to have experienced childhood sexual abuse but had a lower incidence of adult rape than did the VVS group (threefold less) or the control group (fivefold less) [26]. Reissing's two studies suggest that the spasm-based definition of vaginismus is inadequate as a marker for vaginismus, and that fear of pain, pelvic floor dysfunction, and behavioral avoidance need to be included in a multidimensional reconceptualization of vaginismus.

Diagnosis

History

The need to ask every eligible woman at a first encounter visit open-ended questions about pain with intercourse cannot be overemphasized. Having learned that dyspareunia may be an important issue, it may be wise to schedule a follow-up appointment, either to complete the prior issue of the day that has been displaced by dyspareunia or to delve into sexual pain diagnosis and treatment in the near future. Request that the patient

discontinue topical treatments 2 weeks before the visit to improve the accuracy of microscopic examination. It is also important to state up front your neutrality about sexual preference and your desire not to make judgments about sexuality or sexual practices. It is generally helpful for the partner to be present during the evaluation. Most couples experience sexual pain difficulties together, and partners can add insight to the evaluation, and having been part of the assessment, invest themselves more fully in the treatment.

Clinicians find it useful to begin by asking where it hurts, in many cases differentiating superficial from deep dyspareunia early on. If superficial, ask if the pain occurs only when touched or if it occurs all the time, indicating essential vulvodynia. Some patients have difficulty describing anatomic locations, and if a diagram or wall chart is not helpful, it is good to defer localization until the examination. It is important to ask if the pain is also present at times other than intercourse and whether the pain is present on the day of the visit. By Friedrich's criteria, VVS pain should be present on cotton swab touch; however, many patients' pain waxes and wanes, and if the pain has waned, you may not locate the painful area on the day of the visit. There is value in asking the nature of the pain, because pain type is sometimes associated with specific pathology; however, many patients have difficulty finding appropriate descriptors. Although leading questions such as, ''Does it burn?'' can lead to biased answers, it is often necessary. If so, it is helpful to give several options. One study of patients who had vestibulitis found that most VVS patient reports could be summarized as a heat-like sensation or a sharp-like sensation.

Deep dyspareunia is suggested by the sense of ''something being bumped,'' a sense that partners sometimes also attest to. Here also, anatomic location is most helpful. Although most patients cannot tell you their sigmoid colon or urethra hurts, they can usually point to associated stimuli that cause sensations that, if not identical to their dyspareunia, are similar to it. The best example is deep dyspareunia from endometriosis on the sigmoid and adjacent pouch of Douglas, where pain that is experienced after penetration is similar to pain experienced at defecation. Likewise, deep dyspareunia that results from cervicitis can cause crampy pain not unlike menstrual pain. Deep crampy pain that lateralizes may indicate tubal pathology. Of course, in most cases deep dyspareunia warrants pelvic ultrasound and laparoscopy. Conditions that have been associated with superficial or deep dyspareunia are summarized in Table 1 [4].

To determine whether vaginismus is a part of the symptom complex, specific questions must be asked about general body muscle tensing and general and focal pelvic floor muscle tension before and during attempts at penetration. If a patient reports such tensing, it is valuable to ask what their thoughts are at those times. Eliciting a report of fear of self-harm may indicate the potential benefit of desensitizing exercises from a physical or sex therapist once pain has been adequately controlled. Vaginismus in many

Table 1
Physical conditions associated with chronic dyspareunia

Superficial	Deep
Vulvitis, vulvovaginitis	Estrogen deficiency
Bartholinitis	Vaginitis
Condylamata	Mechanical or chemical irritation
Atrophia	Changed vaginal profile
Dermatologic diseases	Scarification
Noninfectious inflammations	Endometriosis exterior/interior
Epithelial defects	Vaginal septum
Large labia minora	Urethritis, cystitis
Vulvar intraepithelial neoplasie	Uterus in retroversion
Vulvar vestibulitis syndrome	Fibroid uterus
Scarification	Ovarian tumor
Size of the penis	Ovarian remnant syndrome
Urethritis, cystitis	Chronic abdominal pain
Anatomic variations	Abdominal wall pain
Hymenal remnants	Irritable bowel syndrome
Episiotomy/rupture/neurinoom	Hemorrhoids
Radiation	

Adapted from Weijmar Schultz W, Basson R, Binik Y, et al. Women's sexual pain and its management. J Sex Med 2005;2(3):301–16.

cases is initiated by superficial pain, and in such cases it is valuable to ask if the onset of inability of penile or other entry was preceded by pain.

A complete medical and surgical history is essential. Usually the relationship between such conditions and dyspareunia is readily apparent, but not always. For example, a sense of vaginal dryness, a frequently reported symptom, can indicate Sjögren syndrome or related dry syndrome. In one report of 22 patients presenting to a dermatology clinic with chronic idiopathic dyspareunia without evidence of vulvovaginal dermatosis or infection, 4 were found to have Sjögren syndrome and 6 had dry syndrome without Sjögren (45% of patients) [27]. Mulherin and colleagues found that among seven women who had chronic dyspareunia attending a tertiary referral service for vulvar disorders who were found to have Sjögren syndrome, the median duration of vaginal symptoms was 7 years, of ocular symptoms 1 year, and oral symptoms 1.5 years, and in all but one woman, dyspareunia presented before other symptoms [28].

Physical examination

On completing a general physical examination, the detailed gynecologic examination is central to narrowing the diagnosis. Note tensing of pelvic muscles on approaching external structures and excessive hydrosis, because these features alert the examiner to the need to proceed with particular care. In this case, it is often valuable to offer to defer the speculum examination in an effort to gather other clinical information, the prospect of which is less frightening.

Visual inspection of the external genitalia suggests the need for biopsy in the case of dysplasia and generally rules out dermatosis. A good general rule is that all unknown or uncertain lesions must be biopsied, but keep in mind that women who have sexual pain are often sensitized and biopsy sites can easily become a focus of pain. To minimize pain a 2-mm punch biopsy is recommended.

Cotton swab testing of the inner labia minora and vestibule is the foundation of diagnosis for superficial dyspareunia. Nineteen years after their introduction, Friedrich's criteria continue to be the defining characteristics of VVS. Instruments developed for measurement of the degree of sensitivity, such as the vulvalgesiometer, are useful only in the research setting. It is helpful to begin testing at the outer portion of the vestibule near Heart line, where pain is often less intense, and proceed toward the hymeneal ring and vaginal mucosa. It is valuable to record findings on a map of the vulva and vagina, as it is not uncommon for pain foci to shift, particularly vaginal tenderness. Vaginal mucosa tenderness is generally not associated with VVS, which is localized to the vestibule, and can indicate a chronic or atypical vaginitis. Collect material from the vaginal walls for saline and KOH wet smear at the same time as testing for tenderness; samples collected from the vaginal pool are less accurate because pool samples can reflect cervical products. Note cervical discharge, ectropion, and tenderness, because the inflamed cervix can be a source of deep dyspareunia.

Digital vaginal examination testing for pelvic wall tenderness should procede in a clock-like fashion, looking for painful urethra and bladder, obturator muscle pain, and rectal pain. In the course of bimanual examination of the uterus and adnexa, be certain to ask whether palpation of each structure reproduces the pain the couple experiences at intercourse.

Saline and KOH wet smear importance cannot be overemphasized. Wiesenfeld showed that these simple and inexpensive tests are frequently not preformed and that the failure to perform office microscopy is the most frequent reason for a missed diagnosis [29]. Nyirjesy and Sobel described a new algorithm for vaginitis evaluation that may help prioritize different diagnoses and suggest appropriate ancillary tests, such as fungal culture [30].

Treatment

Deep dyspareunia

Deep dyspareunia treatments are not always as organ-specific as one might expect. This concept is evidenced in studies showing a substantial improvement in patients who have deep dyspareunia and normal pelvic anatomy without evidence of disease who underwent LUNA and were found to have significant improvement in pain [9]. Nor does deep dyspareunia always decrease following extirpation of the painful structure. Lamvu and colleagues found a 30% improvement in deep dyspareunia following vaginal

apex excision and suggest that the improvement may decrease over time [11]. As an alternative, patients who have vaginal cuff pain may benefit from serial injection of a depo-form of moderate potency steroid and lidocaine into the site of pain, which can often be localized by cotton swab palpation through an open speculum. If resolution is transient, the pain-guided steroid or lidocaine injection, with inclusion of methylene blue dye, can be repeated in the operating room before anesthesia administration, and the blue-stained structure seen on the intra-abdominal side of the vaginal cuff at laparoscopy can be locally excised, limiting the extent of excision and possibly limiting new iatrogenic pain that comes with extirpative surgery.

Laparoscopic correction of uterine retroversion and descent was reported by Yen and colleagues to result in a significant reduction in dyspareunia score ($P < .001$) and an average vaginal lengthening from 5.9 to 7 cm [31]. Carter has reported similar results [32].

The vast majority of women who have superficial dyspareunia are found to have pain at the entry of the vagina and meet diagnostic criteria for VVS. Goetsch has estimated that 75% of women who have dyspareunia are diagnosed with VVS, and more recent studies support that estimate [12,33]. As such, treatments for VVS are applicable to superficial dyspareunia. To date, the highest rate of symptom relief demonstrated in a randomized clinical trial was attained with surgical excision; however, this rather extreme measure should be reserved for intractable cases [34].

Most of the myriad medical treatments have not been studied using prospective randomized controlled trials, and partial relief has been claimed in 40% to 50% of cases regardless of the treatment used. Moreover, analysis of the current recommended treatments underscores the ambiguities in diagnosing vestibulitis. For example, long-term oral antifungal agents have been found by some to result in symptom improvement. Such treatment results would suggest that the underlying disorder in their case is fungal infection. Similarly, symptom relief after cessation of all use of creams, soaps, douches, and other potential irritants suggests that the underlying disorder is an irritant contact dermatitis. Interferon, however (which is somewhat effective in treating genital warts), has been shown to be occasionally effective (rates range from 18% to 100%) in vestibulitis patients. It is not clear why interferon should have an effect, particularly because human papillomavirus (HPV) has been amply demonstrated not to be causally related to vestibulitis [35].

Superficial dyspareunia

Several agents occasionally reported to provide relief must be used with caution, because they can also result in severe contact dermatitis. Although allergic and irritant contact dermatitis are recognized as distinct subsets of vulvodynia, it is clear that patients who have VVS can become sensitized to agents that are repeatedly applied for relief of vestibular pain. Such

agents can include lidocaine in gel or viscous form, topical corticosteroids, and topical antibiotics and antifungals. Dermatitis resulting from such therapy can be so severe as to require short-term high-dose systemic steroids. A thorough and user-friendly listing of potential treatments for VVS has recently been published [35].

Surgical therapies for VVS should be reserved for severe cases that are recalcitrant to conservative therapy. Surgery includes (1) local excision, (2) vestibuloplasty, and (3) total vestibulectomy or perineoplasty. Use of these procedures is based on the theory that painful tissue must be removed and introital dimension increased; a "sham" operation in which, through a small incision, mucosa is undermined and its innervation disrupted (but no painful tissue is excised and no attempt is made to increase the caliber of the introitus) has been shown ineffective. The choice of surgical approach should be individualized based on location and extent of vestibular pain and size and shape of the introitus.

Local excision of painful mucosa can be effective in relieving pain but less so in relieving dyspareunia. Hymenectomy alone, a form of local excision, has been shown to yield a 59% primary success rate. Research by Goetsch has demonstrated an 83% short-term success rate using limited sharp excision and primary closure without vaginal advancement [36]. Vestibuloplasty is a procedure designed to excise the hymen, minor vestibular glands, and painful mucosa of the anterior vestibule but to avoid the extensive dissection and vaginal advancement of vestibulectomy. In this procedure, mucosa and submucosa are incised in a single longitudinal periurethral incision that mobilizes vestibular epithelium at the level of the urethra. The incision is closed transversely using the Heineke-Mikulicz technique to approximate the vagina to Heart line. This leads to a caliber increase of the introitus and vaginal advancement without undermining the vagina. Similar incisions with the same transverse closure can be performed posteriorly, creating increased diameter in the posterior introitus. Total vestibulectomy was first described by Woodruff and Parmley as a modified perineoplasty with removal of the vestibule. The procedure uses a circumferential incision just internal to the hymen (including it in excised tissue) and a second circumferential incision including Heart line laterally, 5 mm below the urethra anteriorly, and posteriorly to the fourchette. The vaginal epithelium is undermined inwardly 2 cm and exteriorized by suturing it to the skin of the perineal body posteriorly and that of Heart line laterally. In patients undergoing vestibulectomy, up to 78 months of long-term follow-up reveals success rates of up to 88%. Vestibulectomy leaves Bartholin glands in situ while covering gland ducts, a potential source of pain. A more definitive procedure combining excision of Bartholin glands with vestibulectomy also has a long-term success rate exceeding 80%. It should be noted that laser vaporization is not indicated for the treatment of VVS, and in fact has led to increased pain.

Vaginismus in many cases is closely associated with VVS. Ter Kuile and colleagues studied women who had lifelong (also known as primary)

vaginismus with respect to VVS diagnostic criteria, comparing them to a control group of women who had superficial dyspareunia [6]. They found that 96% of those who had superficial dyspareunia had pain on touch (as expected) and 69% of vaginismus patients had touch pain. Erythema, the less predictive of VVS signs, was found in 94% of dyspareunia control subjects compared with 77% of lifelong vestibulitis patients, lending support to the concept that the two disorders share some degree of pathophysiology.

Clearly vestibulitis-like pain is an integral part of the experience of most women who have lifelong vaginismus. That said, it is also clear that the behavioral model of vaginismus has therapeutic potential. Ter Kuile and colleagues applied cognitive-behavioral therapy (CBT) techniques, principled on gradual exposure aimed at decreasing avoidance behavior and penetration fear, and sensate focus to 81 women who had lifelong vaginismus [37]. They found that CBT resulted in an increase of intercourse, a decrease in fear of coitus, and an enhancement of successful noncoital penetration behavior. Seo and colleagues began their trial of 12 patients who had vaginismus with functional electrical stimulation (FES) biofeedback and then proceeded to a sexual cognitive behavioral therapy (SCBT) program. After 8 weeks of treatment, all 12 couples had completed the program, had become tolerable to vaginal insertion of larger size probes, and could achieve satisfactory vaginal intercourse [38]. It is not clear from these reports how the investigators helped to reduce VVS pain in their subjects. It should be noted that several recent investigators question the criteria for success used in these studies and suggest that the experience of penetration alone without pleasure is inadequate [4].

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Orgasmic Dysfunction

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Orgasmic dysfunction is a common clinical problem, affecting at least 15% of most populations. A primary care physician sees many women who have orgasmic dysfunction. It is important for primary care physicians to be able to distinguish orgasmic dysfunction from other sexual disorders. A primary care physician should be able to treat simple disorders and refer those patients who require more therapy.

Definitions

There are several different definitions of orgasmic dysfunction. Although all are similar, they differ in some respects. The DSM-IV-TR defines Female Orgasmic Disorder as follows:

> A. Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of Female Orgasmic Disorder should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives.
>
> B. The disturbance causes marked distress or interpersonal difficulty.
>
> C. The orgasmic dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

The DSM-IV-TR further subdivides the disorder into Lifelong Type or Acquired Type; Generalized Type or Situational Type; and Due to Psychological Factors or Due to Combined Factors.

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Lewis reported the conclusions of the committee on Definitions, Classifications and Epidemiology of Sexual Dysfunction of the Second International Consultation. They defined the disorder as follows: ''Orgasmic dysfunction in either men or women is lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation'' [1].

Others have focused on the types of female orgasm. There has been a distinction between coital and noncoital orgasm [2], clitoral versus vaginal orgasm [3], psychologic versus physiologic [4,5], and between real and pretend [6].

These definitions vary in important ways. The DSM-IV definition requires that a patient have a normal excitement phase. The distinction between ''less than reasonable orgasmic capacity'' and ''markedly diminished intensity of orgasmic sensations'' is, of course, subjective, but ''markedly diminished'' seems more severe than ''less than reasonable.'' Neither definition has a measure of intensity or distress.

Bancroft and colleagues surveyed a national probability sample of Black and Caucasian women aged 20 to 65 years. They found that 24.4% of women expressed marked distress about their sexual relationship. In general, the predictors of distress about sex did not fit well with the DSM-IV criteria for the diagnosis of sexual dysfunction in women. Arousal, vaginal lubrication, and orgasm were poor predictors of distress [7]. Nicolson and Burr have questioned the concept of ''normal'' sexual satisfaction. In an in-depth interview study, they found that women's desires and expectations differed appreciably from those reported in the typical clinical and sexologic literature. Women seemed less concerned with experiencing orgasm for themselves, but there was evidence of a strong desire to experience orgasm in this way for the sake of their male partners [8].

Despite the lack of consensus about definitions, the clinician is faced with the need to make a diagnosis. For diagnostic and therapeutic purposes, we think it is critical to distinguish orgasmic disorder from arousal and desire disorders. We therefore agree with the DSM-IV requirement of a normal excitement phase. It is useful to define whether the disorder is acquired or lifelong (or primary or secondary), generalized or situational, and whether there are combined factors. It is sometimes useful to determine if the patient has coital or noncoital orgasm, and if the patient distinguishes vaginal and clitoral orgasms. The degree of distress expressed by the patient may not correlate well at all with the proposed definitions. What is ''reasonable'' or ''marked'' to the physician may not be to the patient.

Epidemiology

A lack of consistent, uniform definitions has hampered epidemiologic studies and outcome studies [9]. Without uniform definition of the disorder, it is difficult to compare treatment regimens, incidences in various

populations, or etiologies and risk factors in different populations. The committee on Definitions, Classifications and Epidemiology of Sexual Dysfunction reviewed the literature and concluded that there was a wide variability in the prevalence of orgasmic function, ranging from approximately 25% in the United States, Australia, and Great Britain to more than 80% in two Nordic countries [1]. Nicolosi surveyed 27,500 men and women from 29 countries and found that 16% of women reported inability to reach orgasm. Simons and Carey conducted a literature review of 52 studies. Pooled current and 1-year figures provided community prevalence estimates of 7% to 10% for female orgasmic disorder, although a lack of methodologic rigor of many studies limited the confidence that can be placed in these findings [10].

Levine reported that 5% of Black women attending a gynecology clinic had never been orgasmic and that 17% had difficulty achieving orgasm [11]. Osborn found 16% of women aged 35 to 59 years in a community survey reported infrequency of orgasm [12]. Rosen reported that 15.4% of women enrolled in a Wellness Center reported difficulty in achieving orgasm [13], and that 10% to 15% of women in community-based studies reported orgasmic disorder [14]. Read reported that 23% of women attending a general medical clinic had anorgasmia [15].

Despite the differences in definitions, it is clear that orgasmic disorder is common in a wide variety of populations, with most large studies reporting that approximately 15% of women report difficulties with orgasm. It is not clear how many of these have difficulty with orgasm as part of an arousal or desire disorder.

Several investigators have attempted to determine risk factors that are associated with orgasmic disorder. Age was not associated with orgasmic disorder in some studies [7,16,17], but others find that older women have increased risk for orgasmic dysfunction [18,19]. Younger age at first orgasm, a greater repertoire of techniques used, having been caressed manually or orally by partners, achievement of orgasm by penile intravaginal movements, attaching importance to sexuality, and being easily sexually aroused were found to be protective against manifest orgasmic dysfunction in a national survey of 18- to 74-year-old Swedish women [16].

Depressive symptoms are associated with orgasmic dysfunction after controlling for treatment and other variables [20]. Antidepressants, particularly SSRIs, are reported to interfere with desire and orgasm. Substance abuse, particularly marijuana and alcohol, is associated with orgasmic dysfunction. The association between drugs and sexual dysfunction is discussed in detail elsewhere in this issue.

There is little published evidence on anatomic or medical problems and orgasmic dysfunction. Clitoral phimosis was not associated with orgasmic dysfunction [21]. Fibromyalgia is associated with a decreased sexual function index [22]. Hysterectomy or vaginal repair has not been associated with orgasmic dysfunction in most studies [23–25]. One study reported

that women who experienced decreased orgasm after vaginal hysterectomy were afraid of disrupting the repair [26].

Dunn and colleagues conducted a study of twins using the Twins UK registry. Complete responses to questions on orgasmic dysfunction were obtained from 4037 women, including 683 monozygotic and 714 dizygotic pairs of female twins aged 19 to 83 years. The interclass correlation coefficients for frequency of orgasm during intercourse and masturbation were higher for monozygotic pairs (31% and 39%, respectively) than for dizygotic pairs (10% and 17%; $P < .0001$), suggesting a clear genetic influence for both [27]. The investigators found that 34% to 45% of the variation in ability to achieve orgasm can be explained by underlying genetic variation, with little or no role for the shared environment [27].

Approach to the patient

History

A detailed history is the key to diagnosing and determining appropriate treatment for patients who have orgasmic dysfunction. A comprehensive review of sexual history taking is provided elsewhere in this issue. As noted previously, various factors may play a role in orgasmic dysfunction. Physical and anatomic problems, medications, substance abuse, sociocultural issues, and interpersonal and individual psychologic factors can all contribute to the dysfunction. It is therefore necessary to screen the patient in all of these areas. Although there is no "central" etiologic factor in orgasmic dysfunction, it seems that in most cases psychologic factors play a prominent role. Anxiety is a key etiologic factor.

When a patient presents stating that she cannot reach orgasm, she often describes the problem in general terms. It is important to learn the *details* of the patient's sexual experiences. If we rely on assumptions and generalities we may miss the essence of the problem. Does the patient have a good understanding of her own anatomy? What is her definition of orgasm? If she reports that she has never had an orgasm, has she ever had enough stimulation? Can she masturbate to orgasm? Is the problem situational? Acquired or lifelong? What specific techniques do she and her partner use? What emotions does she feel during masturbation or coitus? Are there also problems with desire and arousal? Build a detailed description of the presenting problem and rule out other sexual disorders, such as those of desire and arousal, which can also lead to anorgasmia.

Historical data may also be important, particularly how the patient's view of relationships and sex was shaped by the family of origin and early sexual experiences. How did family members relate to each other? Did they express affection? What was the attitude toward sex? Was there sexual or physical abuse? Early losses? This information may give the clinician

some insight into themes and patterns of behavior that may play into the patient's current difficulties.

It is also important to find out how the patient makes sense of the problem. What meaning does it have, and what function might it serve? A common theme is fear of losing control, leading the patient to unconsciously hold back from orgasm. If there is a sexual partner involved, it is often useful to interview the patient and partner together and separately. What is their view of the problem as a couple? What does the problem mean to each of them and to their relationship? What is the affect attached to the problem? Working with the couple allows the clinician to observe the emotional atmosphere of the relationship and assess communication styles. The joint interview may also be the first time the patient and partner have been able to speak openly and explicitly with each other about this sensitive topic and may lead to important insights.

In short, a detailed history and description of the presenting problem is the key in evaluating the patient who has orgasmic dysfunction. The underlying cause may be multifactorial, and psychological factors usually play an important role. Historical data may be helpful, as well as discovering the meaning the problem holds for the patient.

Physical

A complete physical exam should be performed to rule out physical or anatomic problems that may contribute to orgasmic dysfunction. It is rare to find a physical or anatomic cause. Clitoral phimosis is not associated with orgasmic disorder. Some women who have lichen sclerosis report decreased genital sensation and loss of orgasm.

Laboratory evaluation

Laboratory studies are usually not helpful in the evaluation of orgasmic dysfunction.

Diagnosis

The diagnosis is established by history. It is important to distinguish orgasmic disorder from arousal and desire disorders.

Therapy

The interview itself is the first therapeutic intervention and provides a chance to build an alliance, normalize the problem, and validate the patient's experience [27a]. Simple interventions may be helpful, depending on the underlying issues involved. For example, providing basic sex education [28], giving permission to use fantasy [36], and suggesting basic behavioral techniques may be effective [38]. Bibliotherapy has been effective in treating orgasmic dysfunction and is easily implemented in the primary care setting

[29]. Useful books to prescribe include *For Yourself* by Barback (1976) and *Becoming Orgasmic* by Heiman and LoPiccolo (1988).

If more intensive treatment is needed there are several options. As noted previously, research comparing treatment regimens and outcomes is hampered by a lack of consistent, agreed-upon definitions of subjective and objective components of orgasmic dysfunction, and therefore data are limited. Of the following approaches, cognitive behavioral therapy (CBT) has the most positive outcome research [30,39].

Cognitive behavioral therapy

The premise of CBT is that cognition influences feelings and behavior. The patient learns to recognize maladaptive thought patterns and to stop them in their tracks. Goals for CBT in sexual dysfunction include cognitive change, decreased anxiety, increased orgasm, and increased positive thoughts associated with sexual behavior [31a]. Treatment is usually short term, an average of 12 to 15 sessions consisting of visits with a therapist (individual, couples, or group therapy) and behavioral exercises assigned between sessions. Examples of behavioral exercises include directed masturbation and sensate focus exercises [37,38]. Directed masturbation is often used in primary anorgasmia, with success rates in excess of 80%. Success rates for ability to orgasm with a partner is lower, however, approximately 20% to 60% (Heiman, in Principles and Practice of Sex Therapy 2000). Sensate focus exercises are performed with a partner and involve various levels of sensual touching without intercourse or orgasm, thus decreasing performance anxiety. Kegel exercises (ie, contractions of the pubococcygeal muscle) have also been tried, but their effectiveness is controversial [31,32].

Systems theory

This is an approach that accounts for the multifactorial nature of sexual problems. Rather than treating the patient and partner with their individual etiologic factors, you treat the relationship, seeing the couple as part of a complex system within the family and culture.

Psychodynamic psychotherapy

This is traditional, long-term psychotherapy that explores a patient's development, unconscious conflicts, and ego defense mechanisms. There are few outcome data for this approach, which is highly individualized and thus difficult to study.

Pharmacologic therapy and mechanical devices

This is covered in detail elsewhere in this issue. There are no Federal Drug Administration (FDA) approved treatments at this time. The only device that has been approved by the FDA for female sexual dysfunction (including arousal and orgasmic disorders) is the EROS-CTD (Clitoral

Therapy Device; UroMetrics, Inc., St. Paul, Minnesota). This is a small vacuum device designed to increase clitoral engorgement and ability to reach orgasm [33]. A small study of 10 women who had female sexual dysfunction and 9 control subjects found a significant improvement in sensation, lubrication, ability to orgasm, and satisfaction in both groups [34]. A study of 13 irradiated cervical cancer patients who had female sexual dysfunction also found statistically significant improvement in these domains with use of the EROS-CTD device [35].

Summary

Orgasmic disorders are common in women. Unfortunately a lack of consistent, uniform definitions has made this a difficult disorder to study in depth. Etiology is frequently multifactorial, with psychologic issues often playing a prominent role. Diagnosis depends on a detailed history, which then guides treatment to target the underlying causes. Cognitive behavioral therapy has the most favorable outcome evidence to date.

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Female Androgen Insufficiency

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The diagnosis of female androgen insufficiency (FAI) is difficult to objectively quantify because of the lack of a sensitive assay that detects low levels of androgens. Most assays are more specific in measuring hyperandrogenic states than they are in measuring hypoandrogenic states. Because of the multifactorial etiology of androgen insufficiency in women, there is no single, universally accepted management algorithm for women diagnosed with this entity. Androgen therapies currently available, whether oral, transdermal (patch, cream, or gel), or intramuscular, are Federal Drug Administration (FDA) approved only for men, not for women. Testosterone treatments for women when prescribed are done so off label, using products that are FDA approved for men. The only formulation available in the United States for women, an oral estrogen/methyl testosterone formulation, although used for FAI is indicated for postmenopausal women on estrogen therapy who continue to have vasomotor symptoms, and not for sexual dysfunction. Further studies addressing androgen insufficiency in women, including how to objectively confirm the diagnosis and what are the optional treatment interventions, are a research priority.

Female androgen insufficiency

Woman's sexual health, despite its overall importance, has been ignored by the clinical and research community. In the arena of androgens and androgen therapy in women, there has been an even greater dearth of clinical trials work. Scientific research has focused more on the role of androgens in men, because androgen production is much higher in men than in women, and the impact of hypoandrogenism in men can be more objectively assessed

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as compared with women. Data on the effects of androgen decline in women are scant; most research on the role of androgens in women has focused on hyperandrogenic states, such as polycystic ovarian syndrome. Recently, multiple studies addressing female sexual disorders, especially FAI, have reported that androgen loss does occur in women, especially in women after oophorectomy surgery, that there are noted sexual dysfunctions associated with their loss, and that androgen therapy is effective in reversing many of the sexual issues that occur from androgen loss, including amelioration or elimination of the loss of sexual desire and sexual arousal complaints.

Androgens, produced by the ovary and adrenals, are the major sex steroids in men and women, and in both sexes they are responsible for sexually motivational activities. For women, because the ovaries are one of the major producers of androgens, a decline in androgen synthesis often occurs with menopause, such that women lose androgens and estrogens at this stage in their life cycle. The loss of estrogen superimposed on the loss of androgens, especially testosterone, leads to an increase in sexual dysfunction characterized by loss of libido, insertional dyspareunia, and a diminution in sexual desire. In addition to sexual complaints, women often complain of adverse mood changes, muscle wasting, and fatigue that can also be attributable to the loss of androgen and estrogen.

Androgen production and metabolism

In the female, the ovaries and adrenals both play a major role in the biosynthesis of androgens. Of all androgens produced by the female, approximately 20% to 25% come from ovarian sources, 50% from adrenal sources, and 25% to 30% by peripheral conversion in adipose tissue, muscle, and skin. The stimulation for androgen production is regulated by the pituitary gland through luteinizing hormone (LH) for ovaries and adrenocorticotropic hormone (ACTH) for adrenals. The adrenals are able to produce the androgenic steroids dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone (T), and dihydrotestosterone (DHT), whereas the ovaries can produce all of these androgens except DHEAS.

Testosterone is the most significant biologically active androgen in males and in females. It is also a precursor of dehydroepiandrosterone. Ovaries and adrenals produce 50% of testosterone, whereas 50% is contributed by peripheral conversion of androstenedione into testosterone. Androgens are the major precursors for estrogen production also; this production mainly occurs by aromatization of androstenedione to estrone and testosterone to estradiol. Androgens once released into the peripheral circulation bind mainly to sex steroid binding globulin (SHBG) and albumin to some extent; the levels of free or bioavailable androgens are the components of the circulating androgens that can bind to androgen receptors. The quantity of bioavailable androgens, the degree of their binding with SHBG, their affinity to receptors and their

biologic potency, and the degree of peripheral conversion to estrogens and other androgens influence androgen actions in the body [1]. In the unbound state, androgens act not only on genital structures, but also on multiple sites, including the central nervous system, hypothalamus, bone, breast, pilosebaceous unit of skin, skeletal muscle, and adipose tissue.

Variations in SHBG levels directly affect concentrations of free or bioavailable androgens, especially testosterone, which has the highest affinity to SHBG. The administration of exogenous oral estrogens increases the levels of SHBG and consequently decreases the levels of bioavailable androgens, which may in some women create an environment of relative androgen deficiency. SHBG levels also tend to increase with pregnancy, advancing age, cirrhosis, and anorexia nervosa. Drugs that cause an increase in SHBG levels are oral estrogens, such as those in oral contraceptives, excessive thyroid hormone, and some antiepileptic drugs.

Etiology of female androgen insufficiency

There seem to be five etiologic categories of FAI that include ovarian, adrenal, hypothalamic-pituitary, drug-related, and idiopathic. Some diseases like HIV/AIDS, anorexia nervosa, rheumatoid arthritis, systemic lupus erythematosus, and depression also cause decrease in androgen levels and sexual dysfunction in women. The most common cause of androgen deficiency is surgical removal of the ovaries and aging. Other known causes of FAI include any etiology causing ovarian dysfunction, such as natural menopause, chemotherapy or radiotherapy, hysterectomy, adrenal failure, hypopituitism, autoimmune diseases, and anti-androgen therapy [2].

Women who have FAI often present with nonspecific complaints of malaise and fatigue, but can also present with a female sexual dysfunction (FSD). After analyzing multiple cross-sectional studies performed on women at different ages, Braunstein and colleagues found a positive correlation between testosterone levels and sexual arousal, initiation, desire, and frequency of intercourse and sexual gratification [3]. Any condition that leads to a decrease in circulating levels of bioavailable androgens therefore may have a negative impact on sexual wellbeing.

Pathophysiology of androgen production

Davison and colleagues [4] reported a decline in free and total testosterone levels in previously oophorectomized women as compared with normal women after menopause, which infers that surgically menopausal women are at greater risk for FAI. Goldstein and colleagues [5] investigated effects of oophorectomy in laboratory animals. These investigators looked at estrogen effect on urogenital health. Oophorectomy markedly decreased vaginal lubrication and vaginal blood flow, whereas administration of estrogens in oophorectomized animals restored vaginal blood flow and lubrication. They concluded that ovaries play a key role in female sexual health by

maintaining vaginal blood flow and lubrication, thereby decreasing vaginal atrophy and consequent dyspareunia and sexual dissatisfaction.

Miller and colleagues [6] studied the role of decreased androgen levels in women who had hypopituitism with central hypogonadism, as compared with estrogen-depleted or estrogen-replete control subjects. Female androgen levels were consistently lower in women who had hypopituitism than in normal women. The effects of estrogen therapy in premenopausal and postmenopausal women who had hypopituitism were different as compared with women without hypopituitism. That is, androgen levels were lower in women who had hypopituitism even after estrogen therapy as compared with postmenopausal women receiving the same treatment, indicating the importance of pituitary regulation in androgen production.

It seems that female androgen production requires coordination of the ovaries, the adrenals, and the pituitary, and that adequate androgen production ultimately requires an intact hormonal axis.

Changes in androgen levels with age and other medical conditions

Androgens are produced throughout the female reproductive life but have fewer cyclic changes during the reproductive years as compared with estrogens. Androgen production, however, does have a circadian pattern, with production being higher during morning; androgen levels are also associated with the phases of the menstrual cycle. During an ovulatory menstruation cycle, androgen levels show a midcycle increase and then gradually decrease toward the premenstrual phase of the cycle. After the reproductive years, androgen levels are also noted to decline, with the decline beginning as early as the midlife years.

Davison and colleagues [4] conducted a randomized cross-sectional study of 1423 women in Australia to study the effects of natural versus surgical menopause on androgen levels. Steroids assessed in the study were total and free testosterone, dehydroepiandrosterone, and androstenedione. These investigators noted a significant decline in androgen levels with age that was not accompanied by a corresponding change in SHBG levels. Of great interest, the most significant decline in androgen levels was seen in early reproductive years, with subsequent flattening in mid life. During the later years, in comparison with a decline in estrogen levels, there was a small increase in androgen levels in the later years. Menopause in itself did not have a tremendous impact on androgen levels as compared with the marked decline in estrogen levels. Regarding the cyclic changes previously reported occurring during the various phases of the menstrual cycle with an increase noted in androgen levels during mid cycle, these were not observed. Rather, they observed a loss of midcycle increase in androgens that has been associated as occurring in normal young menstruating females. As expected, in oophorectomized women, the levels of testosterone and free testosterone were lower than non-oophorectomized women after menopause, but levels

of DHEA and androstenedione did not seem to be affected. After menopause, androgen production in the ovary is stimulated by persistently elevated levels of luteinizing hormone (LH), which may account for less change in androgen levels as compared with estrogen levels in postmenopausal women. In contrast with the previous studies, this study suggested an increase in SHBG levels after menopause in normal and in oophorectomized women. The effects of uterine excision and bilateral tubal ligation had no significant effect on androgen levels in the women studied. Levels of circulating androgens in this study and the values recorded, however, could be explained by alterations in the adrenal glands and may not reflect a universal ovarian etiology. Further research to determine underlying mechanisms of androgen production and levels throughout the female life cycle is advisable.

Signs and symptoms of female androgen insufficiency

There are many signs and symptoms of FAI, which include muscle wasting, mood changes, fatigue, loss of sexual motivation, and decrease in sexual desire. The most common cause of androgen insufficiency is aging, and it is also associated with a decrease in estrogen levels. Changes in levels of estrogens and androgens seen during menopause and aging have some psychologic and physical effects that include many diverse signs and symptoms. Along with androgens, estrogens also have effects on female sexual health, and their effects are difficult to analyze separately. Not only effects, but their circulation and production are also interrelated. It has been reported that estrogen depletion often results in dyspareunia, sleep disturbances, mood swings, hot flushes, vaginal drying, and atrophy.

Cameron and colleagues [7] suggested some signs and symptoms of FAI, including loss of libido, flattened mood, lack of sexual desire and motivation, and mood changes. Signs of FAI include thinning of pubic hair, osteoporosis, and decreased body mass.

To date, a clinical cluster of FAI recognized by most investigators includes loss of libido, lack of sexual desire and motivation, mood changes, and diminished wellbeing. These symptoms and signs are not found solely in androgen insufficiency, however; they are also seen in many other psychologic and physical conditions other than androgen deficiency. Factors like relationship issues, partner technique, medication, and general health also contribute to sexual health. Because of the multifactorial etiology of FAI, it is difficult to define its clinical scenario.

Diagnosis of female androgen insufficiency

Because female sexuality also has emotional and mental components, the diagnosis and scales to define degree of dysfunction remain obscure, leading to difficulty in interpretation of severity of the problem. Some of the important emotional and mental factors contributing to female sexual wellbeing are anxiety, stress, substance abuse, partner performance, and quality of

relationship. So far, adrenal gland dysfunctions have been considered as the most common cause of FAI.

The diagnosis of FAI consists of a comprehensive sexual history, in some instances laboratory tests for testosterone levels, and exclusion of other medical conditions that may mimic androgen insufficiency. Regarding female sexual dysfunction, psychologic and intrapersonal issues should be ruled out before the diagnosis of FAI is made. Along these lines, a woman can have more than one cause of sexual dysfunction: an intrapersonal issue and FAI. It is therefore important to address all etiologies of sexual difficulty and not assume that one management strategy will lead to amelioration or elimination of the symptoms.

In 2001, the Princeton Consensus recommended diagnosis of FAI be made by history with possible confirmation by measuring serum hormone levels [8].

Decision-making algorithm for initiating androgen therapy in women

Q. Does the woman have symptoms consistent with FAI (eg, low libido and decreased energy and wellbeing)?

A. *If yes, initiate evaluation.*

Q. Is there an alternative explanation or cause for these symptoms (eg, major depression, chronic fatigue syndrome)?

A. *If yes, manage as appropriate. If no, evaluate further.*

Q. Is the woman in an optimum estrogen state?

A. *If yes, continue evaluation. If no, initiate estrogen replacement.*

Q. Does the woman have laboratory values consistent with a diagnosis of androgen insufficiency?

A. *If yes, continue evaluation. This should include assessment of at least two of three measures of total T, free T, or SHBG. Androgen values should be in the lowest quartile of normal ranges for reproductive age women. If no, consider alternative treatments or referral.*

Q. Does the woman have a specific treatable cause for androgen insufficiency (eg, oral estrogens, oral contraceptive use)?

A. *If yes, treat the specific cause (eg, change medications). If no, consider a trial of androgen replacement therapy.*

Their recommendation, however, was that if total free testosterone concentration is measured, that it be measured by equilibrium analysis, which is the gold standard for the assessment of testosterone levels in the low range. In addition to free or total T concentration measurement, the panel also suggested assessment of SHBG level, because this level determines the concentration of bioavailable androgens.

The assessment of androgen production and bioavailability can be done in several ways. These include measurement of free T and SHBG, total T and SHBG, or free and total T. Based on circadian and menstruation effects on androgen production, the panel suggested that clinicians consider measuring T

values at two points, one measurement in the morning and one measurement during the middle of an ovulatory menstruation cycle. In the postmenopausal women, because adequate estrogen is necessary for the preservation of urogenital health, estrogen status should also be assessed.

Braunstein and colleagues [8] proposed an algorithm for the diagnosis of FAI. After proper estrogen supplementation in the estrogen-deprived woman and exclusion of other possible etiologic causes for the sexual dysfunction and other symptoms, the woman should be considered to have FAI. Further evaluation at this point may include laboratory measurement of free testosterone and DHEA-S. For the laboratory assessment of testosterone, equilibrium dialysis is the recognized method; this includes measurement of total T by immunoassay and a dialyzable fraction of T. Another method, though quicker but less reliable than equilibrium dialysis, includes the direct immunoassay measurement of free testosterone using analog ligand. Free testosterone index, sometimes referred to as free androgen index, is an alternative method for the assessment of free T. This index is a ratio of 100 $\times$ total T level/immunoactive SHBG concentration.

Rivera-Woll [1] suggested some other laboratory tests for the diagnosis of FAI besides free and total testosterone and SHBG levels. The immunoassay of DHEA-S is also an easy and reliable method for androgen level assessment. DHEA-S assays are not affected by diurnal variation and also are not bound to SBHG, making them a useful measure for adrenal androgen production assessment, which is especially useful in menopausal women. Other laboratory values to consider include TSH, estradiol, and FSH levels.

Treatments that have been used for female androgen insufficiency

The most controversial aspect of FAI is its treatment. There are many available options for treatment, including medications, counseling, treating underlying causes, sex therapy, vasoactive substances, and estrogen therapy. Some cases of FAI have shown improvement by psychiatric counseling and assurance. Changing sex techniques and solving relationship issues also can be helpful. Despite the use of various therapeutic interventions, there is no standard treatment available for FAI, especially in androgen use.

Hormonal interventions that have been used for the treatment of FAI include combined estrogen and androgen, oral methyl testosterone, testosterone implants and injections, and oral dehydroepiandrosterone (DHEA). The most work with DHEA-S has been done in women who have adrenal insufficiency. Arlt and colleagues [9] studied the effects of dehydroepiandrosterone therapy in women with adrenal insufficiency. They observed significant improvement in physical and psychologic aspects of female sexual health after 4 months' administration of 50 mg DHEA. DHEA is not FDA approved, because its long-term safety and efficacy profile is not well established. Side effects of DHEA treatment are acne, hirsutism, deepening of voice, alopecia, hepatic injury, weight gain, and sleep apnea.

When considering androgen therapy in the reproductive aged woman, virilization of a female fetus is a potential threat, and counseling regarding this should be done. All women receiving androgen therapy should be counseled about potential androgen effects.

Among the available forms of androgens, oral preparations are used most frequently. Injectable preparations of testosterone have disadvantages of extreme peaks and troughs and injection site discomfort. Testosterone creams, sprays, and gels, available for use in men, have been used in women also [10]. Pellet implants are often used in Europe but are infrequently prescribed in the United States. An option used in the United States is combination esterified estrogen/methyl testosterone oral preparations. These are often used in surgically menopausal women and in naturally menopausal ones. Despite the vast research done in the area of the testosterone patch for women, it is not FDA approved in the United States. Many further clinical trials are underway investigating testosterone therapy for women as a treatment for FAI, but it may take years before an FDA approval is obtained.

In 2005, The North American Menopause Society (NAMS) created a position statement regarding the role of testosterone therapy in postmenopausal women [11]. Some of the recommendations supported by NAMS for testosterone therapy are as follows:

- Testosterone therapy should be considered only for postmenopausal women who have symptoms of decreased sexual desire without any identifiable causes.
- Laboratory testosterone levels should not be considered as diagnostic tests for testosterone insufficiency. They should be evaluated for monitoring supraphysiologic testosterone levels before and after initiation of testosterone therapy.
- Serum lipids and liver function tests should be evaluated before starting testosterone therapy in postmenopausal women, and retesting at 3 months should be considered. If the testosterone levels are stable, annual assessment is advised.
- Testosterone therapy is recommended only with concomitant estrogen therapy.
- Testosterone products available in the United States are specifically formulated for men and have very high concentrations of testosterone. Physicians should reduce doses and monitor blood testosterone levels closely for side effects. Transdermal patches and creams may be preferred over pellet and intramuscular formulations to avoid excessive dosing and discomfort.
- Data on efficacy and safety of testosterone therapy do not support testosterone use in women beyond 6 months.
- Testosterone therapy should not be given to women who have breast or uterine cancer or who have cardiovascular or liver disease.

Regarding nonpharmacologic intervention, currently the only FDA approved mechanical device for the treatment of diminished female arousal is a clitoral therapy device that increases blood flow to the clitoris and labia. The mechanism of increased blood flow is hypothesized to improve genital sensation and sexual satisfaction.

Challenges in female androgen insufficiency diagnosis and treatment

The diagnosis and treatment of FAI poses complex diagnostic and management issues for the clinician caring for women [12,13,14]. The most important drawback for the diagnosis of FAI is not only difficulty in measuring accurate testosterone levels at low levels but also a lack of sensitive, standardized, and validated tests for the clinician to easily assess female sexual function in a busy office setting.

Also, some clinicians measure androgen levels and others do not. Current assays for measurement of testosterone levels were developed for high circulating levels in men; therefore, they lack sensitivity in measuring low levels that are found in women. Precise estimation of testosterone concentration is further complicated by lack of normal reference ranges for testosterone levels in women. There are no data available on normal testosterone levels after adjusting for age, menopausal status, and other factors. Another problem for the diagnosis is peripheral biosynthesis of androgens from adrenal androgen precursors, which makes the measurement of androgens more difficult, because these have androgen actions without causing an increase in total androgen levels.

For treatment, several clinical trials have shown improvement in women who have androgen deficiency after androgen therapy [15,16,17]. The understanding of benefits and risks of androgen replacement therapy is evolving. The complexity of female sexuality and factors associated with sexual satisfaction make it difficult to treat androgen insufficiency, because many causes may contribute to symptoms. Counseling and education of women about sexual myths and misconceptions should be a part of the management intervention for all women who have female sexual dysfunction, including women who have FAI.

Because most women who have FAI are diagnosed after menopause, and because most women live one third of their lives after menopause, androgen therapy for symptomatic menopausal women, especially surgically menopausal women, is a high priority for further clinical trials. Clinical emphasis should be placed on the establishment of effective and standardized diagnosis and treatment protocols for FAI.

Summary

FAI, seen commonly and often caused by aging and ovarian dysfunction, still presents a challenge to clinicians because of some unresolved and

unattended aspects of the condition, including standardized diagnosis and management. Although the use of androgens in women who have FAI has been shown to be effective, there are no FDA approved androgen preparations available at this time for women. Large scale, long-term, controlled trials focusing on establishment of valid and standardized diagnosis and treatment options are needed.

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Pharmacological Effects On Sexual Function

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Many commonly used drugs may have effects on sexual function. Currently, there is an intense interest in drug therapy for female sexual dysfunction. It is important for providers to understand the pharmacology of sexual function. This article describes the sexual side effects of common medications and reviews the therapeutic uses of various drugs in sexual dysfunction.

Sexual side effects of common medications

Many commonly used medications may have effects on sexual function. Patients who present with a sexual dysfunction may ask if a medication can cause the dysfunction. The patient will formulate an internal theory of the cause and will first ask the question, ''what's wrong with me?'' The internal theory of the cause may be, ''it's that new drug I am taking.'' It can be difficult to determine if a sexual symptom is an effect of a drug. When a person begins treatment of a chronic condition, there is often a change in self-image. Often one sees any changes in body function as a manifestation of the disease or the treatment. In manufacturer surveys, ''sexual dysfunction'' is often lumped into a single category. Manufacturers often report sexual dysfunction as a ''rare'' or ''uncommon'' side effect. If a side effect is found to be more common in masked placebo-controlled trials or randomized trials between two agents, it can be assumed to be a pharmacological effect of the drug. Not all drug effects have been tested in randomized trials, and

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some drugs have been observed to have effects on sexual function without a randomized trial. A summary of sexual effects reported with common drugs is shown in Table 1.

Contraceptive agents

Reproduction is a profound biological drive. Sexual activity is tied to reproduction on biological, intellectual, and emotional levels. The decision to use contraception is often associated with the decision to become sexually active. The decision to use contraception may come after the decision to become sexually active and may be a self-admission to become sexually active. The ability to be sexually active without fear of pregnancy is relatively new in our society, and the widespread availability of contraception has had profound effects on sexual behavior and beliefs. The relationships between sexual function and contraception are complex. Changes in sexual function related to contraception may involve profound unconscious conflicts about the decision to reproduce.

Combined oral contraceptives

Oral contraceptive use decreases circulating testosterone and increases sex hormone binding globulin, resulting in a decrease in free testosterone [1]. It has been postulated that the decrease in free testosterone results in decreased desire. However, Bancroft and colleagues [2] found no correlation between inhibited sexual desire and testosterone levels, nor that psychosocial issues obscure any relationships between sexual function and testosterone levels [1].

Women often undergo significant life changes concomitant with beginning oral contraceptives that may be associated with changes in desire. Freedom from fear of unwanted pregnancy may lead to heightened desire, and conflict over postponed reproduction may lead to decreased desire. There is little evidence that oral contraceptive use causes decreased desire or other sexual dysfunction, and there is no evidence that changing from one oral contraceptive to another has any effect on sexual function.

Progestin-only agents

There is a large body of literature on the effects of depo-medroxyprogesterone acetate on sexual desire and arousal in men, particularly in sex offenders [3]. Despite its worldwide use as a contraceptive for women, relatively little has been written about its effect on sexual function. Depo-medroxyprogesterone acetate has been reported to cause weight gain, depression, vaginal atrophy, and dyspareunia. Decreased libido has been reported as a side effect in 1.6% to 15% of women [4–6]. One randomized trial compared hysterectomy to progestin therapy for abnormal uterine bleeding [7]. Women

Table 1
Sexual side effects of common drugs

Drug	Type	Quoted side effect[1]
Aceon tablets (2 mg, 4 mg, 8 mg) (Solvay, Marietta, Georgia) Perindopril erbumine	ACE inhibitor	Vaginitis, "sexual dysfunction"
Lotrel capsules (Novartis, East Hanover, New Jersey) Benazepril hydrochloride, Amlodipine besylate	ACE inhibitor	Vaginitis, "sexual dysfunction"
Mavik tablets (Abbott, Abbott Park, Illinois) Trandolapril	ACE inhibitor	Vaginitis, "sexual dysfunction"
Roferon-A injection (Roche Laboratories, Nutley, New Jersey) Interferon alfa-2a, recombinant	Alpha interferon	Sexual dysfunction 1–3%
Catapres tablets (Boehringer Ingelheim, Ridgefield, Connecticut) Clonidine hydrochloride	alpha-adrenoreceptors stimulant	Loss of libido, orgasmic dysfunction
Catapres-TTS (Boehringer Ingelheim, Ridgefield, Connecticut) Clonidine	alpha-adrenoreceptors stimulant	Loss of libido, orgasmic dysfunction
Clorpres tablets (Mylan Bertek, Research Triangle Park, North Carolina) Clonidine hydrochloride, Chlorthalidone	alpha-adrenoreceptors stimulant	Loss of libido, orgasmic dysfunction
Intron A for injection (Schering, Montville, New Jersey) Interferon alfa-2b, recombinant	Alpha-interferon	Amenorrhea, pelvic pain, low libido
Avapro tablets (Sanofi-Aventis, Bridgewater, New Jersey) Irbesartan	Angiotensin II agonist	Decreased libido, impotence (males)
Avapro tablets (Bristol-Myers Squibb, New York, New York) Irbesartan	angiotensin II receptor (AT 1 subtype) antagonist	Decreased libido, impotence (males)
Avalide tablets (Sanofi-Aventis, Bridgewater, New Jersey) Irbesartan, hydrochlorothiazide	angiotensin II receptor antagonist	Decreased libido, impotence (males)

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Table 1 (*continued*)

Drug	Type	Quoted side effect[1]
Xanax XR tablets (Pharmacia & Upjohn, Kalamazoo, Michigan) Alprazolam	antianxiety	Decreased libido
Wellbutrin tablets (GlaxoSmithKline, Research Triangle Park, North Carolina) Bupropion hydrochloride	antidepressant	Decreased libido or no effect
Effexor XR capsules (Wyeth, Madison, New Jersey) Venlafaxine hydrochloride	Antidepressant SNRI	Orgasmic dysfunction, decreased libido
Strattera capsules (Lilly, Indianapolis, Indiana) Atomoxetine hydrochloride	Antidepressant SNRI	Orgasmic dysfunction
Cymbalta delayed-release capsules (Lilly, Indianapolis, Indiana) Duloxetine hydrochloride	Antidepressant SSNRI	Delayed orgasm, decreased libido
Celexa tablets (Forest, New York, New York) Citalopram hydrobromide	Antidepressant SSRI	Delayed orgasm, decreased libido (approximately 1%)
Lexapro tablets (Forest, New York, New York) Escitalopram oxalate	Antidepressant SSRI	Delayed orgasm, decreased libido
Paxil CR controlled-release tablets (GlaxoSmithKline, Research Triangle Park, North Carolina) Paroxetine hydrochloride	Antidepressant SSRI	Delayed orgasm, decreased libido
Paxil tablets (GlaxoSmithKline, Research Triangle Park, North Carolina) Paroxetine hydrochloride	Antidepressant SSRI	Delayed orgasm, decreased libido
Prozac pulvules and liquid (Lilly, Indianapolis, Indiana) Fluoxetine hydrochloride	Antidepressant SSRI	Decreased libido, delayed orgasm
Zoloft tablets (Pfizer, New York, New York) Sertraline hydrochloride	Antidepressant SSRI	Delayed orgasm, decreased libido
Geodon capsules (Pfizer, New York, New York) Ziprasidone hydrochloride	Antipsychotic, dopamine/ serotonin antagonist	Anorgasmia
Risperdal tablets (Janssen, Titusville, New Jersey) Risperidone	Antipsychotic, dopamine/ serotonin antagonist	Orgasmic dysfunction, dry vagina, dyspareunia

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Table 1 (*continued*)

Drug	Type	Quoted side effect[1]
Femara tablets (Novartis, East Hanover, New Jersey) Letrozole	aromatase inhibitor	Hot flashes, vaginal dryness, dyspareunia
Niravam orally disintegrating tablets (Schwarz, Mequon, Wisconsin) Alprazolam	Benzodiazepene	Sexual dysfunction
Cardizem LA extended release tablets (Kos, Cranbury, New Jersey) Diltiazem hydrochloride	Calcium channel blocker	Sexual dysfunction
Norvasc tablets (Pfizer, New York, New York) Amlodipine besylate	calcium channel blocker	Sexual dysfunction
Tarka tablets (Abbott, Abbott Park, Illinois) Trandolapril,verapamil hydrochloride	Calcium channel blocker	Decreased libido
Tiazac capsules (Forest, New York, New York) Diltiazem hydrochloride	Calcium channel blocker	Impotence
Evoxac capsules (Daiichi, Montvale, New Jersey) Cevimeline hydrochloride	cholinergic agonist	Hot flashes, amenorrhea, dyspareunia, orgasmic dysfunction
Mirapex tablets (Boehringer Ingelheim, Ridgefield, Connecticut) Pramipexole dihydrochloride	Dopamine agonists	Impotence
Campral tablets (Forest, New York, New York) Acamprosate calcium alcohol abstinence	Ethanol avoidance	Vaginitis, sexual dysfunction, decreased libido
Zoladex (AstraZeneca,Westboro, Massachusetts) Goserelin acetate	GNRH agonist	Hot flashes, decreased libido, dyspareunia, orgasmic dysfunction
Zoladex 3-month (AstraZeneca,Westboro, Massachusetts) Goserelin acetate	GNRH agonist	Hot flashes, decreased libido, dyspareunia, orgasmic dysfunction
Lupron injection pediatric (TAP, Deerfield, Illinois) Leuprolide acetate	GNRH agonsist	Hot flashes, decreased libido, dyspareunia, orgasmic dysfunction
Lupron Depot-PED 7.5 mg, 11.25 mg and 15 mg (TAP, Deerfield, Illinois) Leuprolide acetate	GNRH agonsits	Hot flashes, decreased libido, dyspareunia, orgasmic dysfunction

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Table 1 (*continued*)

Drug	Type	Quoted side effect[1]
Vantas (Valera, Cranbury, New Jersey) Histrelin acetate	LH-RH agonist	Decreased libido
Pravachol tablets (Bristol-Myers Squibb, New York, New York) Pravastatin sodium	lipid-lowering compounds	Low libido
Eskalith CR controlled-release tablets (GlaxoSmithKline, Research Triangle Park, North Carolina) Lithium carbonate	Lithium salt	Anorgasmia – one trial showed no effect in women
Lithobid tablets (JDS, New York, New York) Lithium carbonate	Lithium salt	Anorgasmia – one trial showed no effect in women
Eldepryl capsules (Somerset, Tampa, Florida) Selegiline hydrochloride (MAO inhibitor)	MAO inhibitor	Transient anorgasmia
Cialis tablets (Lilly ICOS, Indianapolis, Indiana) Tadalafil	PDE5 inhibitor	No proven effect in women
Viagra tablets (Pfizer, New York, New York) Sildenafil citrate	PDE5 inhibitor	No proven effect in women
Revatio tablets (Pfizer, New York, New York) Sildenafil citrate (used for pulmonary hypertension)	PDE5 inhibitor approved for pulmonary artery hypertension	No proven effect in women
Lotronex tablets (GlaxoSmithKline, Research Triangle Park, North Carolina) Alosetron hydrochloride	Serotonin 5HT3 receptor antagonist	Sexual dysfunction
Symbyax capsules (Lilly, Indianapolis, Indiana) Olanzapine, Fluoxetine hydrochloride	SSRI, benzodiazepene	Delayed orgasm, decreased libido

[1] Side effects quoted from manufacturer's literature. See text for detailed explanations of clinical trials.

treated with hysterectomy reported fewer problems with sexual desire and interference with sex than those treated medically.

Injectable progestins can lead to atrophic vaginitis and dyspareunia. Treatment with local estrogen cream can alleviate this symptom. Injectable progestins may increase the risk of decreased libido but there is little evidence that they have other effects on sexual function in women. However, if a woman complains of a sexual dysfunction while on an injectable progestin, it is reasonable to discontinue the progestin and change to another form of contraception. It would be wise to explore the patient's desire for children and determine of there is a conflict about the use of a contraceptive.

Antihypertensives

Antihypertensives and cardiac drugs can affect sexual function by acting on the central or peripheral nervous system, the vascular system, or by having hormonal effects. Adrenergic inhibiting drugs, diuretics, vasodilators, monoamine oxidase inhibitors, antiarrhythmics, hypolipidemics, and digitalis may affect the sexual response. Adrenergic inhibiting drugs have been reported to have the most serious effects in men and women [8].

Alpha-adrenergic agents such as clonidine and prazosin have been reported to reduce desire in women in a small randomized trial [9]. Clonidine has been shown to reduce subjective and physiological arousal in women as measured by a vaginal plethysmograph [10]. In the Treatment of Mild Hypertension Study, no difference in sexual dysfunction in women was found between placebo and one of five drugs (acebutolol, amlodipine maleate, chlorthalidone, doxazosin maleate, or enalapril maleate) [11].

The sexual effects of antihypertensive drugs have been more intensively studied in men than women [12], with erectile dysfunction the most commonly studied effect. However, these drugs may have similar effects on the excitement phase in women, leading to failure of arousal and lubrication. Hanon and colleagues [13] reported that in a survey of patients treated for hypertension, sexual dysfunction was reported by 49% of men and 18% of women ($P < .01$). "Interest for sexuality" was decreased for 41% of women, and sexual pleasure was decreased for 34%. In another survey, Watts [14] reported that a higher percentage of men who had hypertension presented drug-induced sexual problems than did women. Sexual dysfunction before treatment is reported to be common in women who have hypertension [15]. A recent abstract [16] reported that 42% of women who had hypertension reported sexual dysfunction compared with 19% who have had normal blood pressure [16]. Thirty-three percent of the treatment-naïve women had sexual dysfunction versus 48% of women receiving treatment of hypertension ($P = .27$). Treated women who had normal blood pressure had higher rates of sexual dysfunction than those who had poorly controlled hypertension [16]. It seems that sexual dysfunction is common in treated women

who have hypertension. It is probable that hypertension and hypertensive treatment both have effects on sexual function in women.

Hypertension and hypertensive therapy is common in women. Still, little is known about the sexual effects of antihypertensive drugs in women. The author suggests that if a woman complains of a sexual problem that develops while taking an antihypertensive drug, her complaint should be taken at face value. A sexual history should be taken, but if no other obvious cause for the dysfunction is found, modification of her therapeutic regimen should be considered. However, there is little outcome-based evidence to guide a change in regimens. It would seem wise to avoid alpha-adrenergic agents in women who complain of sexual problems. Based on reported evidence from men, changing to an angiotensin II receptor agonist might be useful [17,18].

Antiepileptic drugs

Sexual dysfunction is reported to be common in patients who have epilepsy and are on an antiepileptic drug. In one trial, women who were initially treated with or were switched to lamotrigine had a significantly improved change in sexual functioning, both globally and in five sub-categories (desire/frequency, desire/interest, pleasure, arousal/excitement, and orgasm) [19]. Gabapentin has been reported to induce orgasmic dysfunction in case reports [20–23]. Topiramate has been reported to cause reversible anorgasmia [24].

Psychoactive drugs

Antidepressants

Sexual dysfunction is common in the general population, but is more common in people who have depression. Many antidepressant drugs are reported to affect sexual function [25]. However, controlling for pre-existing sexual dysfunction is difficult. Lack of sexual desire is a symptom of depression, and treatment of depression may improve sexual desire [26]. A drug could have less effect on sexual desire because it is a more effective antidepressant.

Commonly used selective serotonin reuptake inhibitors are reported to inhibit desire and impair orgasm (see Table 1). In a European survey of 502 adults taking a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine receptor inhibitor (SRNI), Williams and colleagues [27] reported that 34.2% of men and 32.5% of women were classified with antidepressant-induced sexual dysfunction.

Duloxetine and paroxetine have a significantly higher incidence of acute treatment-emergent sexual dysfunction when compared with placebo. However, the incidence of acute treatment-emergent dysfunction for duloxetine is

significantly lower than that observed for paroxetine [28]. In a study by Detke and collegues [29], the incidence of acute treatment-emergent sexual dysfunction in patients treated with duloxetine or paroxetine was 46.5% and 62.8%, respectively.

There may be some advantages for bupropion, moclobemide, nefazodone and reboxetine over other antidepressants [25]. Bupropion has been reported to have fewer sexual side effects than SSRI drugs in several clinical trials [30]. Significantly more women treated with sertraline [30,31] or fluoxetine [32] had orgasmic dysfunction than those treated with bupropion or placebo.

The optimal treatment of SSRI-associated sexual dysfunction has not been established. A meta-analysis concluded that the available evidence was limited [33]. Switching to bupropion may be beneficial, but it is important to consider and address other causes of sexual dysfunction.

Antipsychotic agents

Sexual dysfunction is common in patients who have psychiatric diseases [34]. It may be difficult to distinguish the effects of a drug from the effects of the disease. Antipsychotics increase serum prolactin [35], which can lead to amenorrhea and a hypogonadal state. High serum prolactin is associated with decreased sexual desire.

Frequency of sexual dysfunction was reported to be high with haloperidol (38.1%) and also with olanzapine (35.3%), quetiapine (18.2%), and risperidone (43.2%) [36]. Olanzapine was reported to have less effect on libido than other neuroleptics [37,38]. In another study, Kim and colleagues [39] reported that female patients who had schizophrenia and experienced menstrual disturbances, galactorrhea, or sexual dysfunction on risperidone were switched to olanzapine. Prolactin levels fell significantly and patients reported a decrease in amenorrhea, improved cycle regularity, and a decrease in sexual side effects. Quetiapine is also reported to have a low incidence of sexual side effects [40].

Antianxiety agents

Little has been reported about sexual side effects of the benzodiazepines. Midazolam use has been reported to be associated with sexual fantasies [41]. Alprazolam [42], lorazepam [43], and diazepam [44] have been reported to be associated with sexual dysfunction in case reports. However, there are no large trials that have reported increased incidence of sexual dysfunction with these drugs.

Lithium

Lithium has been reported to have no effect on sexual function in bipolar patients [45].

Gonadotrophin releasing hormone agonists

Gonadotrophin releasing hormone agonists suppress the release of gonadotropins if they are given in a continuous dose. As a result, they lead to a hypogonadal state. Prolonged use leads to vaginal atrophy and can lead to dyspareunia, decreased desire, and orgasmic dysfunction.

Illicit/recreational drugs

The relationships between illicit/recreational drug use and sexual function are complex. Adolescents may experiment with recreational drugs and sex simultaneously or serially [46]. Patients who have sexual dysfunctions may use drugs to self-medicate. Patients who have substance abuse are more likely to have a history of childhood sexual abuse [47,48], and thus may be more likely to have sexual dysfunctions. Women who are substance abusers may exchange sex for drugs or money to buy drugs [49]. Many patients who abuse one drug also use other drugs, making it difficult to separate the effects of different drugs [50]. Randomized controlled trials of the effects of illicit drugs on sexual behavior are difficult or impossible to perform.

It is important to determine if a patient who has a sexual dysfunction also has a substance abuse. Successful treatment of the dysfunction will usually require treatment of the substance abuse. Successful treatment of the sexual dysfunction may help in the treatment of the abuse and may prevent relapse of substance abuse [51].

Alcohol

Alcohol is known to decrease inhibitions and is popularly believed to increase sexual desire. Population studies show that heavier drinkers are more likely to be sexually active and are more likely to have had more than one sexual partner in the previous year [52]. Encounters with new partners are more likely to involve alcohol [53]. However, studies of alcohol's effects on sexual function show that acute alcohol intoxication decreases libido, interferes with arousal, leads to failure of erection and ejaculation, and impedes orgasm in women [54–56]. Chronic alcohol abuse leads to a hypogonadotrophic state and loss of sexual function in men and women [57]. Alcohol may be used to self-medicate perceived problems with sexuality [55].

The relationships between alcohol use and sexual dysfunctions are complex and not completely understood. Women who present with sexual problems should be screened for alcohol abuse. Women who have coexisting alcohol abuse and sexual dysfunction should be treated for alcohol abuse. Physicians should never recommend alcohol as a treatment of sexual problems.

Marijuana

In a community epidemiological study of 3004 adults, inhibited orgasm and painful sex were associated with marijuana use after controlling for demographics, health status variables, and psychiatric comorbidity [58]. Marijuana use was linked to sexual behavior in college undergraduates [59]. Marijuana was reported to be ineffective in relieving sexual problems in patients who had amyotrophic lateral sclerosis [60] but some patients who had multiple sclerosis reported improved sexual function [61]. It is likely that marijuana's sedative effects impair sexual arousal and orgasm.

Cocaine

It is a popular belief that cocaine use increases sexual desire and arousal. However, the available evidence shows that use of crack cocaine is associated with decreased sexual desire in women [62–65]. Cocaine use has been reported to lead to hyperprolactinism and sexual dysfunction [66].

Cocaine use is associated with family drug use, first age of sexual abuse, age of first depressive symptoms, and age of first illicit drug use [48]. Sexual abuse in childhood, penetrative sexual abuse in childhood, and sexual abuse by a family member in childhood were significantly associated with lifetime crack cocaine use [47].

The relationships between cocaine use and sexual behavior are complex. Many of the identified risk factors for cocaine use are also risk factors for sexual dysfunction. Women who use cocaine may have increased numbers

Table 2
Drugs used to treat sexual dysfunction in women (off label use)

Drug	Sexual dysfunction		Comment
Estrogen	Dyspareunia		Meta analysis shows beneficial effects [74]
	Hypoactive disorder	desire	One randomized trial showed beneficial effect [76]
Testosterone	Hypoactive disorder	desire	Several clinical trials show beneficial effect in adequately estrogenized women who were surgically menopausal [77–80]
Oral methyl testosterone	Hypoactive disorder	desire	Two trials show benefit in women who were dissatisfied on estrogen alone [81,82]
DHEA	Hypoactive disorder	desire	Benefit only in adrenal insufficiency [86]. No benefit in perimenopausal women with low desire
Sildenafil	FSAD		Conflicting trials. Large randomized trials showed no benefit [87–91]
Bupropion	Hypoactive disorder	desire	Benefit in some trials. In one trial, women showed increased arousability but not desire [93,94]
Apomorphine	FSAD		No proven benefit
Yohimbine	Various		No proven benefit

of sexual partners, and those who exchange sex for drugs or money have a greater number of sexual partners [49]. Exchanging sex for drugs or money impairs desire and performance. Chronic cocaine use probably leads to decreased sexual desire and impaired orgasm as an independent effect.

Amphetamines

Amphetamines are popularly believed to increase sexual desire [67]. In healthy volunteers, desire and satisfaction were moderately to profoundly increased by MDMA in more than 90% of subjects. Orgasm was delayed and erection was impaired [68]. Amphetamine use is correlated with sexual activity in youths [69]. Amphetamines are often found in drug screens of victims of sexual assault [70,71].

Narcotics

Some women in methadone treatment report that they believe that heroin increases their libido and sexual performance [64]. Narcotics have been reported to cause decreased sexual desire and can lead to amenorrhea [51]. Sexual dysfunction is common in methadone-substituted addicts [34]. Higher doses of methadone are associated with decreased frequency of sexual contact and orgasm in women [72].

Drugs used to treat sexual dysfunctions

History

Throughout recorded history, there has been a search for an effective aphrodisiac. An astounding variety of substances have been touted to increase desire, arousal, or potency. None have survived scientific scrutiny, but there are still a great number of herbs and other substances that are sold to increase sexual function. There are also several medications that have been used to treat sexual dysfunctions. Drugs used to treat sexual dysfunction in women are shown in Table 2.

Estrogen

There is a high correlation between serum estradiol levels and sexual function in women. The Yale Midlife Study showed that significantly more women who have an estradiol level of less than 50 pg/ml reported vaginal dryness and dyspareunia than did those who have a level greater than 50 pg/ml. Women who have an estradiol level of less than 35 pg/ml reported reduced sexual activity [73]. Several investigators have shown that topical and systemic estrogen therapy improves vaginal atrophy, restores normal elasticity, and increases vaginal fluid secretions and blood flow. The Women's Health Osteoporosis Progestin and Estrogen trial demonstrated relief of vaginal atrophy with

systemic doses of 0.45 mg oral conjugated equine estrogen both with and without 2.5 mg or 1.5 mg medroxyprogesterone acetate, and 0.3 mg conjugated equine estrogen with and without 1.5 mg medroxyprogesterone acetate. A meta-analysis that evaluated randomized controlled trials from 1969 to 1995 found that compared with placebo, estrogens given by the oral or vaginal route significantly improved symptoms, dyspareunia, and vaginal pH. When oral and vaginal estrogens were compared, vaginal products had greater patient acceptance and higher systemic estradiol concentrations but insignificant improvement of dyspareunia and pH changes [74].

Although estrogen therapy is clearly beneficial for dyspareunia and vaginal dryness, the effects of estrogen therapy on libido are less clear. Menopausal status has been shown to be related to decreased sexual desire [75] One randomized trial has shown that estrogen therapy had a significantly positive effect on mood, sexual desire enjoyment, and orgasmic frequency [76].

Transdermal testosterone

Several randomized clinical trials have shown that transdermal testosterone in a dose of 300 μg/day increases sexual desire in surgically menopausal women who are taking replacement estrogen [77–80]. Women who were randomized to testosterone in a dose of 300 μg/day reported increased frequency of intercourse and increased pleasure/orgasm when compared with placebo. Doses of 150 μg/day were less effective and doses of 450 μg/day appeared to have increased side effects with little increase in effectiveness.

Although statistically significant, the effects of transdermal testosterone on frequency of intercourse are relatively small. There is an appreciable placebo response noted in all of the studies. In a study by Busters and colleagues [79], there was an increase in frequency of intercourse compared with baseline of 1.56 episodes/4 wk in the treatment groups and 0.73 episodes/4 wk in the placebo group. Simon and colleagues [78] observed a similar increase from baseline in the frequency of total satisfying sexual activity of 2.10 episodes/4 wk in the testosterone group compared with 0.98 episodes/4 wk in the placebo group. In all trials, women randomized to testosterone reported greater satisfaction with intercourse.

Potential concerns of testosterone therapy include virilization (hirsutism, acne, voice deepening, alopecia), liver toxicity, and adverse effects on lipoproteins. Data from clinical trials in women suggest that testosterone therapy is well tolerated; most reported adverse effects are mild. Virilization effects are dose related and not associated with all routes of administration. For example, virilization only occurs in a small percentage of patients receiving transdermal testosterone. Furthermore, oral substituted testosterones are associated with liver toxicity and increases in high-density lipoprotein whereas transdermal or subcutaneous administration do not appear to have these effects. Hirsutism is a concern for many women. In Shifren and colleagues' [80] trial, hirsutism was assessed using a Lorenzo scale and no

difference was observed between any dose of testosterone and placebo. However, women on the 300 μg dose used facial depilation significantly more often when compared with baseline, placebo, or the 150 μg dose.

All published randomized trials of transdermal testosterone therapy are in women who have had an oophorectomy, and have included controls that were treated with estrogen. The effect of transdermal testosterone therapy in menopausal women who are not on estrogen replacement, are naturally menopausal, or are premenopausal who have hypoactive sexual desire disorder is also not known.

The Food and Drug Administration recently considered approval of a testosterone patch for treatment of hypoactive sexual desire disorder in women who have had an oophorectomy and are on adequate estrogen therapy. The drug was not approved because of concerns about long-term safety. No drug has been approved for the treatment of hypoactive sexual desire disorder.

Other androgens

Oral methyl testosterone in combination with esterified estrogens is available in the United States. Several investigators have explored the use of the combination in women who have hypoactive sexual desire. Sarrell and colleagues [81] randomized women who were dissatisfied with their estrogen-only hormone replacement to estrogen-only or estrogen plus testosterone. Women randomized to the estrogen-androgen preparation reported increased desire and sexual sensation. Lobo and colleagues [82] found that treatment with the combination of esterified estrogens and methyltestosterone significantly increased the concentration of bioavailable testosterone and suppressed sex hormone binding globulin (SHBG). Sexual interest or desire were increased from baseline with combination treatment and were significantly increased compared with esterified estrogens alone. Warnock and colleagues [83] compared the effect of combined esterified estrogens (1.25 mg) and methyltestosterone (2.5 mg) versus esterified estrogens (1.25 mg) alone for 8 weeks in surgically menopausal women who had diminished sexual interest. After 8 weeks, significant differences between treatments were not seen in the Changes in Sexual Functioning Questionnaire sexual desire/interest subscale score, which was the primary efficacy variable. In contrast, statistically significant between-treatment differences were found for several secondary efficacy variables including Menopausal Sexual Interest Questionnaire sexual interest/desire score, arousal/erection subscale score and Women's Health Questionnaire sexual functioning subscale score. This study exemplifies some difficulties seen in pharmacological studies of sexual function in women. Frequency of intercourse seems to be too crude a measure of sexual function, but scales that measure desire, interest, or satisfaction may not be appropriate for all populations and can give contradictory results in the same population.

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) have been postulated to be beneficial in sexual desire in women [84]. DHEA and DHEAS levels decline with aging. Oral DHEA administration results in increases in serum DHEA, DHEAS, androstenedione, testosterone and dihydrotestosterone, and estradiol and estrone in postmenopausal women [85]. In women who have adrenal insufficiency, DHEA supplementation significantly increased the frequency of sexual thoughts, sexual interest, and satisfaction with both mental and physical aspects of sexuality [86]. In normal postmenopausal women, DHEA supplementation has been shown to have an effect on sexual function only in the 70 to79-year-old group. This effect may be related to decreased adrenal function in the older population.

PDE 5 inhibitors

Penile erection during sexual stimulation in men is caused by increased penile bloodflow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide from nerve terminals and endothelial cells, which stimulates the synthesis of cyclic guanosine monophosphate (GMP) in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased bloodflow into the corpus cavernosum.

Inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cyclic GMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation. There are several drugs available in the United States that inhibit PDE5. None of these have been approved for use in women.

Randomized trials of PDE5 inhibitors in women have been contradictory. In a double blind placebo-controlled study, 202 women who had sexual arousal disorder were randomly assigned to 50 mg sildenafil (adjustable to 100 mg or 25 mg) or placebo. Genital sensation during intercourse or stimulation, and satisfaction with intercourse and foreplay, significantly improved after 12 weeks of sildenafil compared with placebo [87]. Sildenafil has been reported to improve arousal and orgasm in symptomatic [88] and asymptomatic women [89]. However, a study of 577 estrogenized and 204 estrogen-deficient women who were diagnosed with female sexual arousal disorder (FSAD) and randomized to sildenafil or placebo showed no significant benefit of the drug [90].

One study, by Basson and colleagues [91], reported on the use of a vaginal photoplethysmograph to measure effects of sildenafil in estrogenized postmenopausal women in a randomized placebo-controlled trial. Sildenafil improved neither arousal nor orgasm. However, subsequent analyses comparing high versus low vaginal pulse amplitude responders revealed significantly reduced latency to orgasm, and increased subjective sexual arousal and perception of genital arousal in the latter group. The authors suggest

that female sexual arousal disorders might be heterogenous, and that the plethysmograph might be useful in determining which women might respond to sildenafil.

There is little outcome-based evidence that PDE5 inhibitors are effective in treating female sexual dysfunctions, and they are not approved for that indication in the United States. It is not clear which women if any might benefit from the use of PDE5 inhibitors. The use of PDE5 inhibitors in women for treatment of sexual dysfunctions cannot be recommended.

Antidepressants

Antidepressants have been used to treat sexual dysfunctions. In women, bupropion has been reported to improve hypoactive sexual desire associated with SSRI use [92]. In a randomized trial of men and women who have sexual dysfunction, significantly greater improvements were noted on the libido and global assessments of sexual functioning in a bupropion group than a placebo group after 12 weeks. Sixty-three percent of the bupropion-treated patients reported themselves much or very much improved, compared with 3% for placebo. Changes in sexual behavior were much less dramatic [93]. In another sequential controlled trial of nondepressed women and men, bupropion had significantly better effects on all measured aspects of sexual function in women, and significant improvements relative to placebo ($P < .05$) in overall sexual satisfaction and with intensity of orgasm [94]. Bupropion has been reported to have significant effects on sexual arousal, orgasm completion, and sexual satisfaction in premenopausal women who have sexual desire disorder [95, 96].

It appears that bupropion may have a beneficial effect on desire and orgasm in some women. It is not yet clear which women may benefit, or if the effect is independent of the antidepressant effect.

Apomorphine

Two small studies have addressed the effects of apomorphine on sexual dysfunction in women. In one study [97], 24 women who had orgasmic sexual dysfunction were enrolled in a prospective randomized crossover protocol. Sexual response was evaluated objectively (duplex ultrasound) and subjectively (self-reported questionnaire) following vibrator stimuli with the addition of 3 mg sublingual apomorphine or placebo. Apomorphine seemed to produce more subjective and objective changes in the sexual arousal phase of women who had orgasmic sexual dysfunction than placebo. In another study, 6 of 50 women who had arousal disorders and hypoactive sexual desire disorder responded in a 4-week taken-as-needed, open-label, dose-escalation regimen starting at 2 mg or 3 mg of apomorphine. The nonresponders were randomly allocated to treatment in one of six possible sequences of three 2-week double blind, crossover study periods with

apomorphine 2 mg or 3 mg, washout, and placebo. Orgasm, enjoyment, and satisfied by frequency scores improved during treatment with daily apomorphine compared with baseline and placebo [98].

Yohimbine

Yohimbine is an alpha2 adrenergic receptor antagonist that stimulates norepinephrine release. It has been used for the treatment of erectile dysfunction [99], but has been reported to have only modest efficacy [100]. There are few reports of yohimbine use in women. Yohimbine was reported to have no obvious effect in women who have hypoactive sexual desire [101]. It has been recommended as an ''antidote'' for SSRI-induced sexual dysfunction [102–104] based on open uncontrolled trials. In a controlled trial, yohimbine was not superior to placebo in relieving SSRI-associated sexual dysfunction [105].

There is little outcome-based evidence that yohimbine is effective in female sexual dysfunction, whether spontaneous or associated with SSRI use. Until such evidence is available, the use of yohimbine in female sexual dysfunction cannot be recommended.

Summary

Many drugs may have effects on sexual function. Sexual function is complex and psychological and relationship issues are likely to have greater impacts on sexual function in women than drugs. Although it is important to understand the effects of drugs on sexual function, physicians should use caution in ''medicalization'' of sexual function in women [106].

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Sexual Function after Gynecologic Cancer

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Although the impact of gynecologic cancer and its treatment on sexual function is often unrecognized, sexual functioning is the most enduringly compromised quality of life issue these women face. For many women who have gynecologic cancer, life after cancer treatment includes learning to cope and serious long-term sexual problems. This article endeavors to increase awareness of sexual health after gynecologic cancer and provide information in an effort to address and treat sexual concerns.

Prevalence of sexual dysfunction

The long-term cancer survivor population continues to grow. More than 62% of adults and 77% of pediatric cancer survivors live beyond 5 years. Cancer is viewed by many as a chronic disease with multifaceted sequelae, including physical, psychosocial, and vocational issues. More than 900,000 women diagnosed with primary gynecologic malignancies within the past 20 years are alive today [1]. Treatment-related survival gains are frequently accomplished by side effects that may diminish quality of life. Common sexual functioning issues include loss of sexual desire, dyspareunia, loss of sensation in the genital area, and decreased ability to achieve orgasm.

Andersen and colleagues studied the prevalence of sexual dysfunctioning in women with early-stage gynecologic cancer [2]. Forty-seven patients were evaluated for sexual difficulties before treatment and again at 4, 8, and 12 months post-treatment. Multiple screening tools were used to evaluate each type of sexual function. The presence of sexual dysfunctions based on *The Diagnostic and Statistical Manual for Mental Disorders* (DSM-III)

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was noted; sexual dysfunctions included dyspareunia, inhibited desire, inhibited excitement, and inhibited orgasm. Patient outcomes were compared with outcomes of women who had benign gynecologic disease (n = 18) and healthy control subjects (n = 57). At time of 12-month follow-up, all sexual problems were more prevalent in women who had a history of gynecologic cancer but who did not have a history of sexual dysfunction. Of importance, approximately 50% of these women were diagnosed with at least one sexual dysfunction.

Additional data have been provided by Stewart and colleagues in a survey of 200 women who had a history of ovarian cancer [3]. Participants were a minimum of 2 years post-treatment and were recruited from cancer clinics and community organizations in the United States and Canada. Respondents to a mailed survey answered questions relating to physical, psychologic, and overall well-being. Almost 60% of respondents noted that their sex lives had been negatively affected by their cancer. Younger and married women reported more negative effects of cancer treatment. Seventy-five percent of the women characterized their sex lives as "adequate to poor." Twenty percent of the women reported "moderate" sense of loss about their sexuality, whereas approximately 26% experienced a "great" sense of loss about their sexuality. Both studies demonstrate the widespread sexual dysfunctioning in patients treated for gynecologic malignancies.

Barriers to addressing sexual health after gynecologic cancer

Time constraints and lack of communication between the patient and her health care professional are barriers to addressing sexual health after gynecologic cancer. Recognition of research regarding the impact of gynecologic treatments on sexual function is also lacking [4].

A recent study conducted in the United Kingdom queried 27 physicians and 16 nurses treating women who had ovarian cancer [5]. Although most of the respondents believed that women would experience a sexual problem during treatment for ovarian cancer, only 25% of physicians and 20% of nurses reported actually discussing sexual functioning with their patients. Reasons listed for not discussing sexual function included:

A feeling that "it is not my responsibility",
Lack of knowledge and experience,
Embarrassment, and
Lack of resources to provide support if needed.

Impact of gynecologic cancer treatment on sexual function

Patients who have gynecologic cancers often undergo multiple treatments, including radiation, hysterectomy with or without oophorectomy, vulvectomy, or chemotherapy. Pelvic radiation is associated with vaginal

dryness and pain. During a radical hysterectomy, a portion of the upper vagina is removed, decreasing vaginal length. Removal of the ovaries is accompanied by decreases in estrogen and testosterone, increasing vaginal dryness and decreasing sexual desire, respectively. Vulvectomy results in anatomic changes that may affect sexual function. The side effects of chemotherapy, such as fatigue, nausea, and vomiting, may decrease well-being and may interfere with sexual function. Chemotherapy can also induce menopause and subsequent sexual problems in young premenopausal women.

Impact of treatment for cervical cancer on sexual function

The evaluation of cervical cancer treatment on women's sexual functioning continues to progress. An early study by Abitbol and Davenport evaluated changes in vaginal anatomy and sexual function [6]. Participants included women who had a history of cervical cancer who received radiotherapy (n = 28), underwent surgery (n = 32), or received both treatment modalities (n = 15). Approximately 75% of women treated with radiotherapy alone reported vaginal shortening or narrowing compared with less than 1% of women who received surgery alone. In patients receiving radiotherapy and surgery, 60% reported some vaginal changes and 33% reported experiencing sexual dysfunction. This study provides some insight into the effect that pelvic radiation may have on sexual function in women who have a history of cervical cancer.

Additional data were provided by Bergmark and colleagues, who compared women who had a history of cervical cancer with women who did not have a previous malignancy [7]. In this study conducted in Sweden, women who had been treated for early-stage cervical cancer 5 years before the study (n = 332) and women who had no history of cancer (n = 489) were surveyed about specific vaginal changes and sexual function using a questionnaire. Sexually active women who had a history of cervical cancer reported experiencing moderate or substantial reduction in vaginal length, moderate or substantial reduction in vaginal elasticity, moderate or much superficial dyspareunia within the last 6 months, and moderate or much deep dyspareunia within the last 6 months. Furthermore, the women who had a history of cervical cancer reported much distress with regard to vaginal changes and problems with intercourse.

Frumovitz and colleagues compared quality of life among cervical cancer survivors treated with single modality therapy and age- and-race-matched female control subjects [8]. Inclusion criteria were age younger than 55 years, stage 1 disease, survival of more than 5 years post-treatment, lesions less than 6 cm, and squamous, adenosquamous, or adenocarcinoma histologies. Quality of life was evaluated by the Short Form – 12 (SF-12), Brief Symptom Index – 18 (BSI-18), Abbreviated Dyadic Adjustment Scale (ADAS), Cancer Rehabilitation Evaluation System Dating Subscale (CARES), and Female Sexual Functioning Index (FSFI).

One hundred fourteen patients (37 surgery, 37 radiotherapy, 40 control subjects) were included for analysis. When compared with surgery patients and control subjects using univariate analysis, radiation patients had significantly poorer scores on standardized questionnaires measuring health-related quality of life [9], psychosocial distress, and sexual functioning. The disparity in sexual function remained significant in a multivariate analysis. Univariate and multivariate analyses did not show significant differences between radical hysterectomy patients and control subjects on any of the outcome measures.

The investigators concluded that cervical cancer survivors treated surgically have better self-perceived physical health, less psychologic distress, and better functioning than patients treated with radiotherapy. These data suggest that patients treated surgically have no difference in quality of life, sexual functioning, or psychologic distress than age- and race-matched control subjects.

Consequences of oophorectomy

Surgical removal of the ovaries is associated with decreases in estrogen and testosterone and triggers immediate menopause in premenopausal women. Low levels of estrogen are associated with vaginal dryness, pain, and itching. Testosterone insufficiency has been associated with decreased sexual desire. Testosterone levels have been shown to decrease to approximately one half of those before surgery [10]. As a result, many women who undergo bilateral oophorectomy report decreased sexual functioning.

Predictors of sexual inactivity in women who have ovarian cancer

Sexual functioning has also been studied in women who have ovarian cancer. Carmack Taylor and colleagues evaluated 232 women who had epithelial ovarian cancer [11]. Forty-seven percent of the women were receiving active treatment; 53% were undergoing surveillance. Approximately one half of the participants had not engaged in sexual activity during the previous month. Of the women who were sexually inactive, 44% reported not having a partner. Thirty-eight percent reported lack of interest. Other predictors were physical problems that impeded sexual activity, fatigue, or partner problems. Women were more likely to be sexually active if they were married ($P < .001$), younger than age 56 years ($P < .001$), under surveillance ($P < .01$), and liked the appearance of their bodies ($P = .004$). Univariate analyses indicated that demographic, psychosocial, and medical factors are significantly associated with sexual functioning or satisfaction, sexual frequency or habit, and sexual discomfort. The investigators recommended that sexual rehabilitation for patients who have ovarian cancer should address the management of physical and psychologic symptoms and also should include the patient's partner when appropriate.

Psychosocial factors contributing to sexual problems after gynecologic cancer

Depression and anxiety caused by cancer and its treatment negatively affect sexual function. Fear of cancer recurrence or its causing problems with sexual activity can prevent patients from resuming sexual activity after treatment. Poor self-image caused by changes in weight or disfiguring surgery may contribute to sexual problems after gynecologic cancer.

Psychologic variables and sexual function in women who have ovarian cancer

Psychologic variables, such as depression, anxiety, liking the appearance of one's body, and the ability "to feel like a woman," are also correlated with levels of sexual functioning [11]. In the same study of ovarian cancer patients, depression was associated with decreased sexual functioning and satisfaction, increased discomfort, and decreased sexual frequency. This study clearly underscores the importance of assessing physical and psychologic problems in women who have sexual dysfunction after gynecologic cancer.

Psychosocial counseling after gynecologic cancer

Patients and their partners should receive counseling before treatment for gynecologic cancer to address fears, myths, and what to expect with regard to their sexual function. After treatment for gynecologic cancer, referral to a sex therapist or relationship counselor may be beneficial in women who experience sexual dysfunction. The American Association of Sex Educators, Counselors and Therapists [12] can assist with identifying a credentialed sex therapy professional. Education on the female sexual response cycle and female anatomy can be used to help women define what is considered normal. Communication and sensate focus training with a partner can help couples resume sexual activity after treatment. Anxiety reduction techniques can address issues such as fear of causing harm during sexual activity or fear of cancer recurrence. For women of reproductive age, distress over the loss of fertility or femininity may have a negative impact on sexual function. Assisting women with improving body image after cancer treatment can have a positive impact on their ability to engage in sexual activity. It may be beneficial to include a woman's partner in psychosocial counseling.

Pharmacotherapies

Estrogen insufficiency after an oophorectomy is associated with vaginal dryness or hot flashes, causing sexual concerns and decreasing quality of

life. These symptoms can be treated by way of systemic or local estrogen administration with products indicated for vaginal atrophy. Some data support the use of testosterone therapy in women who have decreased sexual desire after an oophorectomy. There are no testosterone therapies approved by the U.S. Food and Drug Administration for use in women. Although there may be risks associated with hormone therapy use in patients who have had gynecologic cancer, the use of hormone therapy can improve quality of life and can provide palliative relief. The risks and benefits of hormone therapy should be evaluated and discussed with each and every patient. Prescription or nonprescription vaginal lubricants can be used to reduce dryness. Pain medications can be used to help relieve discomfort that may be interfering with sexual activity.

Use of clitoral device after cervical cancer treatment

Schroder and colleagues evaluated cervical cancer patients who underwent pelvic radiation and had self-reports of sexual arousal or orgasmic problems ($n = 13$) [13]. Subjects were instructed to use a battery-operated clitoral device four times weekly during foreplay and self-stimulation for 3 months. Outcomes were measured using the Female Sexual Function Index (FSFI), Derogatis Interview for Sexual Functioning, and Dyadic Adjustment Score. Significant improvements in all domains of the FSFI were observed after 3 months of treatment, suggesting that women who have arousal or orgasm problems after gynecologic cancer may benefit from clitoral vacuum therapy. These findings warrant a larger, controlled clinical trial. Several other trials suggest that the phosphodiesterase inhibitors improve female sexual arousal [14]; however, these have not been evaluated in gynecologic cancer patients.

Vaginal dilator therapy

Pelvic radiation is associated with vaginal dryness, fibrosis, and stenosis that can interfere with sexual function or pelvic examinations. Vaginal dilator therapy or regular intercourse can be used to maintain a functional vagina and aid in detection of any future problems. An appropriately-sized dilator, fitted by a physician, is used in an outpatient setting. Some patients may experience less pain using dilators of gradually increasing size. Dilatation should occur three times per week for 10 minutes each episode. Dilator therapy should be continued for a minimum of 3 years after completion of gynecologic cancer treatment. Patients should be educated on the importance of compliance on the treatment outcomes. Patients should also be reassured that use of a dilator does not lead to a recurrence or spread their cancer. Alternatively, frequent sexual intercourse can also improve vaginal alterations.

Discussing sexual function with gynecologic cancer patients

The most important step in initiating a conversation on sexual function is direct physician inquiry. This lets patients know that it is acceptable to discuss any sexual concerns and conveys physician comfort with the topic. A general, open-ended question can be used to initiate the conversation. Questions can also be tailored for specific treatment paradigms. Examples of such questions include the following:

- "Since your ovaries were removed, have you experienced any changes in your desire for sex?"
- "Many cancer survivors notice changes or problems in their sex lives after cancer treatment. Do you have any problems or concerns related to sexuality?"
- "Women who undergo pelvic radiation often experience vaginal dryness that can make intercourse uncomfortable. Has this been a problem for you?"

A graduated counseling system

The PLISSIT model of sex therapy is a graduated counseling system that can be used in initiating and maintaining a conversation on sexual function [15]. There are four levels of approach in the model that allow the health care provider to determine at which level he or she can provide treatment for sexual dysfunction within his or her level of expertise, referring to a specialist when needed. The four parts of the PLISSIT are:

- Permission giving — letting patients know that sexual concerns are common and that it is appropriate to discuss sexual concerns
- Limited information — providing brief education on impact of cancer and treatment on sexual function
- Specific suggestions — providing resources for information, suggestions to improve sexual activity, and information on interventions
- Intensive therapy — initiating long-term individualized therapy or referral to a physician specializing in sexual dysfunction, a sex therapist, or marital counseling

This model can be particularly helpful when used by nurse practitioners to determine the level of dysfunction and subsequent steps for addressing concerns.

Diagnosing sexual problems in patients who have gynecologic cancer

An assessment of sexual problems should evaluate a woman's sexual history before and after treatment for gynecologic cancer. A validated sexual history questionnaire should be completed by the patient. Risk factors, such as type of surgery, menopause status, medications, depression, and

any other chronic illnesses, should be taken into consideration. It is important to establish if the problems are situational, acquired, or lifelong. Next, a complete physical examination should be conducted. Laboratory testing may be indicated in some situations. Open communication between the patient and health care provider is essential.

Ways to stay sexually healthy

The American Cancer Society suggests several key points for patients to remember regarding sex life during or after cancer treatment [16]. Sharing this information with patients may help women dealing with sexual issues and may break the ice when discussing sexual concerns. There are several points to keep in mind as one tries to continue one's sex life during or after cancer treatment.

- Talk to your doctor about sex and tell your partner what you've learned. Strive for good communication about sex with your partner and with your doctor, otherwise your partner may fear that sex will hurt you. If you feel weak or tired and want your partner to take a more active role in touching you, say so. If some part of your body is tender or sore, you can guide your mate's touches to create the most pleasure and avoid pain.
- Do not deny yourself just because your usual routine has been changed. Those times can be a chance to learn new ways to give and receive sexual pleasure. You and your partner can help each other reach orgasm through touching and stroking. At times, just cuddling can be pleasurable. You could also continue to enjoy touching yourself. If both partners cannot reach orgasm while the man's penis is inside the woman's vagina, they may feel cheated. Keep an open mind about ways to feel sexual pleasure. Some couples have a narrow definition of what is normal in sex. For people treated for cancer, however, there may be times when intercourse is not possible.
- Talk with your doctor, nurse, or any other member of your health care team. Learn as much as you can about the usual effects of your cancer treatment on sexuality. When you know what to expect, you can plan ways of dealing with those issues. If you are too embarrassed to ask your doctor whether you can have sex, you may never find out.
- For people who have cancer, sexual touching is often a satisfying experience. Pleasure is possible, even if some aspects of sexuality have changed. Few cancer treatments (other than those affecting some areas of the brain or spinal cord) damage the nerves and muscles involved in feeling pleasure from touch and reaching orgasm. No matter what kind of cancer treatment you have, the ability to feel pleasure from touching almost always remains. For example, women whose vaginas are painfully tight or dry can often reach orgasm through stroking of their breasts and outer genitals.

- Eating right and exercising can keep your body strong and your spirits up. Practice relaxation techniques, and seek professional help if you think you are depressed. Boost your self-esteem. Remind yourself about your good qualities. If you lose your hair, help yourself look and feel good physically by wearing a wig, hat, or scarf if you are more comfortable with them.

Resources

Many patients are reluctant to ask questions of their health care team or mention sexual problems. In addition to broaching the topic of sexual concerns, patients may benefit from self-help books on the topic of sexual function for cancer survivors. The American Cancer Society has published two books on sexuality after cancer, one for men and one for women (*Sexuality & Cancer: For the Woman Who Has Cancer and Her Partner*; for a free copy call the American Cancer Society at 1-800-ACS-2345) [16]. The book *Sexuality and Fertility After Cancer* by Leslie R. Schover, PhD (John Wiley & Sons, 1997) is also an excellent resource [17]. The booklet *Ovarian Cancer: Sexuality and Intimacy* is available for free by contacting The National Ovarian Cancer Coalition at 1-888-OVARIAN or www.ovarian.org.

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