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19 Female sexual dysfunctions: Future of medical therapy

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Abstract

Female sexual dysfunction (FSD) is age related, progressive and highly prevalent, affecting up to 20% to 43% of women in the fertile age, and 48% of the older postmenopausal women. Pelvic floor disorders are among the most important and yet neglected medical contributors to womens' sexual dysfunctions. However, sexual dissatisfaction, disinterest and even dysfunction may be appropriate within an "antisexual" context (for example, a partner affected by Male Sexual Disorders or abusive) and they should not be labelled per se as "diseases" or dysfunctions requiring medical treatment. FSD may occur with or without significant personal distress. Sociocultural factors may further modulate the perception, expression and complaining modality of a sexual disorder. The meaning of sexual intimacy is a strong modulator of the sexual response and of the quality of

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satisfaction the woman experiences; the quality of feelings for the partner and partner's health and sexual problems may further contribute to FSD. Co-morbidity between FSD and medical conditions - urological, gynecological, proctological, metabolic, cardiovascular and neurological disorders - is beginning to be recognized and addressed. The progressive understanding of the pathophysiology of women's sexual function and dysfunction is stimulating the research on potential pharmacologic treatments. This chapter will briefly review the pathophysiology of women's sexual function and dysfunction, and focus on clinical use of hormonal (hormone therapy (HT), tibolone, testosterone patches) and non-hormonal agents including those impacting the central nervous system (CNS), such as bupropion, flibanserin, and bremelanotide, in the treatment of FSD. New perspectives on genital treatments: hormonal (vaginal estrogens, vulvar testosterone) and non hormonal (vasoactive drugs, botulin toxin) will be briefly considered.

1. Introduction

Women's sexuality has only recently emerged as a central concern in the medical community. It is multifactorial, based on biological, psychosexual and context-related factors, correlated to couple dynamics and family and sociocultural issues [1]. It requires anatomical and physiological integrity of the "somatic body" and its continuous interactions with the "psychic mind", which has solid neurobiological bases [2,3]. Indeed, it involves a complex sequencing of interrelated mind/body processes [4]. The etiology of female sexual dysfunctions (FSD) is exceedingly complex. Few treatment options exist that address the complex multilayered etiological determinants of FSD [4]. Further investigations are needed to better understand all the pathways of women's sexual behaviour, always considering the role of the biological and medical factors in the appropriate psychosexual and sociocultural context [4-11].

Key aspects of women's sexual functions and dysfunctions will be summarized with the clinical perspective of an updated sexual medicine. Biochemistry and neuroendocrine aspects of women's sexual response should nevertheless be integrated with an accurate symptom's description and physical examination to get the diagnostic complexity of the biological conditions potentially associated with FSD.

This chapter will briefly review the physiology of women's sexual function and dysfunction, and focus on clinical application of both hormonal and non-hormonal agents, including central nervous system (CNS)-acting agents, in the treatment of FSD. New perspectives on genital treatments will be briefly considered.

2. Women's sexual physiology

A concise review of women's anatomy and physiology is a necessary pre-requisite for a better understanding of biological contributors of women's sexual function and dysfunction and the potential targets of new drugs for FSD [1]. For women's sexual function, a physiologic response requires the integrity of the hormonal, vascular, nervous, muscular, connective and immune systems [12]. During sexual stimulation, the genital female sexual arousal response is elicited by sensory stimulation as well as central nervous system activation. A normal sexual response requires the anatomic and

functional integrity of the brain's entire limbic system (role of initiation of sexual desire and related sexual phenomena). This culminates in a series of vasocongestive and neuromuscular events leading to physiological changes, as vaginal lubrication, increased length and width of the clitoris, engorgement of the labia as well as increased sensitivity of the genitals.

2.1. Role of the central nervous system

The human sexual response involves three major functions of the CNS:
1) **Neurovegetative**, which coordinates all the autonomic responses preparing the body to the intercourse; 2) **Affective**, which sets-up the emotional scenario (positive or negative) accompanying the sexual stimulus and context-related factors (including the potential partner attitude and/or response); and 3) **Cognitive**, which helps the subject to evaluate the wish and risks of behaving sexually.

The **hypothalamus** is the key center of the autonomic nervous system [12]. Different areas of the hypothalamus are involved, modulating the vascular and cardiac response, the breathing changes, changes in pheromone secretion, and changes in some neurohormones pattern secretion. A set of nuclei known as the interstitial nuclei of the anterior hypothalamus are specifically involved. The hormone oxytocin is produced by these nuclei in a cyclic pattern of secretion in fertile women: this represents the base of the physiological discontinuity of female sexuality, both during the regular menstrual cycle as well as during major reproductive life events such as pregnancy, puerperium, abortion, and menopause. At the same time, there is a peak in pheromone receptivity during ovulation in women, in association with an overall greater level of odor discrimination ability during the years of fertility. After menopause, odor discrimination ability in women decreases significantly and much resembles physiologic male levels [13-17]. Pheromones may be responsible for rhinencephalon mediated interactions in the mid-cycle variations observed in women, which may in turn be triggered by the ovulatory androgen peak, promoting the atresia of non-dominant follicles in the ovary as well as a mental and physical peak in sexual desire, arousability and receptivity. The biologic ramification of these mid-cycle changes is to increase female sexual responsiveness when the likelihood of conception is at its highest.

The **limbic** area (paleo cortex) seems to modulate the emotional-affective state (happiness, depression, anxiety, fear) accompanying the perception of sexual desire and central arousal and correlated sexual behaviours [18]. Indeed depression lowers sexual desire and central arousability [19]; anxiety has a bimodal effect: in small doses it may increase sexual desire (as it happens in the light anxiety of the first phase of falling in love) whilst at higher levels (typical of performance anxiety, present in women as well as in men) it has a prominent inhibitory effect, affecting arousability and specifically affecting the vascular systemic and genital response.

The **neo-cortex** is involved in the sexual response in humans as a final target of sensory inputs which arrive from the different sensory organs (sensitive stimulation). An important role in the sexual function is referred to brain dimorphism. Prenatal and postnatal endocrine patterns – testis determining factor (TDF) and its expression – and their interactions with environmental factors, modulate the neurobiological basis of gender dimorphism and its implications in sexual function [1,20,21].

Quality of brain functioning, sexual and non-sexual, depends on the complex pattern of connections between neurons, their continuous plasticity, and the intensity by which they are stimulated through affective events, educational level, and environmental challenges. The sexual response is coordinated by many neurotransmitters, such as monoamines (dopamine, norepinephrine, and serotonin), neuropeptides (opioid peptides), neurohormones (oxytocin and vasopressin) and neurotrophins (including the Nerve Growth Factor, NGF). It has been demonstrated that there are regional and quantitative differences in neurotransmitter's activities as a consequence of brain dimorphism, basis of a different sexual response and behaviour [1,13,20].

At the level of the **spine**, sensory stimuli relevant to sexual function are conveyed by neural sympathetic, parasympathetic and somatic pathways consisting of pudendal, pelvic and hypogastric nerves and the lumbosacral sympathetic chain [1,22].

2.2. Role of women's genital anatomy and physiology

In addition to the brain's activity and neuromodulation, the anatomical and physiological integrity of women's genitalia is obviously needed for the appropriate sexual response. Their integrity is a necessary although not a sufficient condition for a physiologic physical response and a satisfactory activity.

The vagina is the key organ of women's **physical receptivity**. The quality of vaginal trophism is mediated by the level of **tissue estrogens** [23]. This contributes to:

1) the **mucosal trophism**, wall elasticity and resistance to coital microtraumas;
2) the **responsiveness of perivaginal vessels** as mediator of the genital arousal, leading to **vaginal vasocongestion and lubrication**, and **congestion of periurethral vessels** [24,25]. The latter is key to protect the urethra from the "mechanical trauma" of intercourse in non-aroused conditions or when the genital arousal is blocked by pain, leading or contributing to vaginal dryness, dyspareunia and post-coital cystitis, appearing 24 to 72 hours after the intercourse.
3) the vaginal **ecosystem**, with the leading role of Doderlein bacilli, which is responsible for the maintenance of vaginal acidity at pH around 4, thus contributing to the biological defense of the vagina against invasive germs, mostly saprophytic pathogens of colonic origin [23].

During sexual quiescence, the vagina is a potential space with an H-shaped transverse cross-section and an elongated S-shaped longitudinal section. Grafenberg described the **G (Grafenberg) spot** of the anterior vagina along the urethra and stimulation of this spot gave special sexual pleasure and orgasm for the women [26]. Perry and Whipple named this sensitive area the Grafenberg, or G spot, in honour of Dr. Grafenberg [27,28]. Other investigators could not locate a spot, but found, rather than a spot, a general excitable area along the whole length of the urethra running along the anterior vaginal wall [29]. Recent ecographic evidence has substantiated the presence of a "G spot" in women reporting intense vaginal arousability and vaginal orgasms [30].

The **pelvic floor muscles influence** sexual function in women [17,22]. The levator ani's tone, strength and performance are a major contributor to vaginal receptivity and responsiveness, coital competence and pleasure, and for the orgasmic muscular response.

Orgasm may involve rhythmic contractions of the pelvic striated circumvaginal musculature, often with concomitant uterine and anal contractions.

The integrity and dynamic responsiveness of vaginal vessels to sexual stimuli, mediated through the neurovascular pathways, is a key contributor of genital arousal response. Factors –such as smoking, cardiovascular diseases, hypertension, diabetes, atherosclerosis - affecting the integrity of vessels may contribute to FSD, especially to genital arousal disorders [31-33]. During female sexual arousal the blood flow to the genitals is increased in the clitoris, the bulbocavernous bodies, labia and the vagina leading to vasocongestion, engorgement and lubrication.

Vaginal lubrication is a consequence of the increased blood flow in perivaginal vessels. During the non-aroused state the anterior and posterior walls are normally collapsed and touch each other. Nevertheless, they do not adhere as they are covered with a thin layer of basal fluid allowing them to separate easily. The fluid is a mixture of secretions from the whole genital tract: it's mainly vaginal plasma - transudate mixed with desquamated cervical and vaginal cells and cervical secretion. The vaginal transudate is formed from the blood, slowly circulating through the capillaries supplying the vaginal epithelium [24,25]. A plasma filtrate from the blood leaks out of the capillaries into the interstitial tissue space. In the vagina the fluid then passes through the epithelium. In the sexually unstimulated state the vaginal fluid has a higher K^+ and lower Na^+ concentration throughout the phases of the menstrual cycle [34]: there is a slow passage through the epithelium and in balance with reabsorption, which leads to the just moist vagina, but not moistened enough to allow penetration without pain.

During **sexual arousal**, the blood flow to the vaginal epithelium is rapidly increased as a consequence of neural innervation via the sacral anterior nerves - the parasympathetic pathway (pelvic nerve). The increased blood flow results in an increased volume of ultrafiltrate percolating between the vaginal epithelial cells, saturating the reabsorption capacity and thereby the excess of fluid accumulates at the vaginal surface as a clear, slippery and smooth lubricant, moistening the vagina so painless penetration and thrusting is possible. Despite many inaccurate accounts in physiology textbooks, vaginal lubrication during sexual arousal does not occur from increased secretion of vaginal glands [34]. Activation of the sympathetic nervous system occurs during the later stages of arousal and orgasm and is responsible for the increase in heart rate and blood pressure in women[35].

During the **arousal response** there is a relaxation of the trabecular smooth muscle in the clitoris and the clitoral blood flow increases. This leads to a rise in intra-clitoral pressure with increased tumescence and engorgement [24,35-37]. As the tunica of the clitoris is elastic, no veno-occlusive mechanism occurs as it is seen in the penis.

There is still a preliminary knowledge of which mediators are crucial in the regulation of female genital arousal response. Several adrenergic, cholinergic and nonadrenergic-noncholinergic (NANC) neurotransmitters/mediators have been identified in the female genital tract (adrenaline, acetylcholine, vasoactive intestinal polypeptide (VIP), nitric oxide synthase, neuropeptide Y, calcitonin gene-related peptide, substance P, pituitary adenylate cyclase activating polypeptide, helospectine and peptide histidine methionine [24,25,34]. VIP has traditionally been considered the most important neurotransmitter in the regulation of vaginal blood flow [24], but nitric oxide (NO) has

also been identified as an important mediator of increased blood flow to the female genitals during arousal based on human and animal studies [38]. However, the exact roles of these and other neurotransmitters/mediators in the physiological and pathophysiological arousal response still need further investigation.

3. Female sexual dysfunctions: Summary of clinical aspects

Three major dimensions (**Female Sexual Identity**, **Sexual Function** and **Sexual Relationship**) interact to give to women's sexual health its full meaning or its problematic profile [39-41]. Women's sexuality is discontinuous throughout the life cycle and is dependent on biological (reproductive events) as well as personal, current contextual and relationship variables.

FSD is age related, progressive and highly prevalent, affecting up to 20% to 43% of women in the fertile age [19], and 48% of the older women, still sexually active in the late postmenopause [42], FSD may occur along a continuum from **dissatisfaction** (with potential integrity of the physiologic response but emotional/affective frustration) to **dysfunction** (with or without pathological modifications), to severe pathology, biologically rooted. Pelvic floor disorders are among the most important and yet neglected medical contributors to womens' sexual dysfunctions [43]. However, sexual dissatisfaction, disinterest and even dysfunction may be an appropriate response to an "antisexual" context (for example, a partner affected by Male Sexual Disorders or abusive) and they should not be labelled per se as "diseases" or dysfunctions requiring medical treatment. FSD may occur with or without significant personal distress [42,44]. **Sociocultural factors** may further modulate the perception, expression and complaining modality of a sexual disorder. The **meaning of sexual intimacy** is a strong modulator of the sexual response [14,17] and of the quality of satisfaction the woman experiences; the quality of feelings for the partner and partner's health and sexual problems may further contribute to FSD [42].

Co-morbidity between **FSD and medical conditions** - urological, gynecological proctological, metabolic, cardiovascular and neurological disorders - is beginning to be recognized. For example, desire disorders have an important comorbidity with depression. Moreover, according to the epidemiological survey of Laumann, urinary tract symptoms have a RR = 4.02 (2.75-5.89) of being associated with arousal disorders and a RR=7.61 (4.06-14.26) of being associated with sexual pain disorders [45].

3.1. Classification of FSD

Over the last decades, classification of FSD has undergone intense scrutiny and revisions, which mirrors the new understanding of its complex etiology. Until a decade ago, the classification of FSD, which constitutes the frame of reference for an appropriate diagnosis, was focused almost entirely on its psychological and relational components. Indeed, FSD were included in the broader manual of "psychiatric" disorders (Diagnostic Statistic Manual of Mental Disorders, DSM III R 1987, DSM IV TR, 2000). The first and second consensus conferences on FSD set out to define women's sexual dysfunction with special attention to bringing together the current levels of evidence with definitions fitting women's wording and experiences. The latest classification from the consensus conference is reported in **Box 1** [46].

Box 1. Classification of Female Sexual Disorders.

Women's sexual interest / desire disorder

There are absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivations (here defined as reasons/incentives), for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be more than that due to a normative lessening with the life cycle and length of a relationship.

Sexual aversion disorder

Extreme anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity

Subjective Sexual Arousal Disorder

Absence of or markedly diminished cognitive sexual arousal and sexual pleasure from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur.

Genital Sexual Arousal Disorder

Complaints of absent or impaired genital sexual arousal. Self-report may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from non genital sexual stimuli.

Combined Genital and Subjective Arousal Disorder

Absence of or markedly diminished subjective sexual excitement and awareness of sexual pleasure from any type of sexual stimulation as well as complaints of absent or impaired genital sexual arousal (vulval swelling, lubrication).

Persistent Sexual Arousal Disorder

Spontaneous, intrusive and unwanted genital arousal (e.g. tingling, throbbing, pulsating) in the absence of sexual interest and desire. Any awareness of subjective arousal is typically but not invariably unpleasant. The arousal is unrelieved by one or more orgasms and the feelings of arousal persist for hours or days.

Women's Orgasmic Disorder

Despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation.

Dyspareunia

Persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse.

Vaginismus

The persistent or recurrent difficulties of the woman to allow vaginal entry of a penis, a finger, and/or any object, despite the woman's expressed wish to do so. There is often (phobic) avoidance and anticipation/fear/experience of pain, along with variable involuntary pelvic muscle contraction. Structural or other physical abnormalities must be ruled out/addressed.

Adapted from [46]

For a more accurate definition of the sexual symptoms, health care providers should also briefly investigate the so called "descriptors" of the disorders, as defined by the International Consensus Conferences held in 1998 and 2003 [46,47].
Main descriptors include:

a) The **etiology of the disorder**, further detailed in predisposing, precipitating and maintaining factors. Each category includes biological, psychosexual and contextual causes.

   - **Biological causes** include hormonal dysfunctions, pelvic floor disorders, cardiovascular problems, neurological conditions (particularly pain related), metabolic disorders (diabetes), affective disorders (depression and anxiety). All the medical conditions that may directly or indirectly affect sexuality, through their multisystemic impact and/or the consequences of the pharmacologic, surgical and/or radiotherapic treatment, should be considered in the differential diagnosis of potential contributors to the reported FSD. Loss of sexual hormones, consequent to natural or iatrogenic menopause, is a major contributor to FSD [42].
   - **Psychosexual causes** refer to emotional/affective/psychic factors such as negative upbringing/losses/trauma (physical, sexual, emotional) [48], body image issues [49], binge eating disorders affecting self-esteem and self-confidence, attachment dynamics (secure, avoidant, anxious) that may also modulate the level of trust in the relationship, the intensity of the commitment, the confidence in loving and attitude towards affective and erotic intimacy.
   - **Contextual descriptors** include past and current significant relationships [50], current interpersonal difficulties, partner's general health issues and/or sexual dysfunctions, inadequate stimulation and unsatisfactory sexual and emotional contexts;

b) The **disorder being generalised** (with every partner and in every situation) or **situational**, specifically precipitated by partner related or contextual factors, which should be specified [46,47]. Situational problems usually rule out medical factors that tend to affect the sexual response with a more generalized effect [40].
c) The **disorder being lifelong** (from the very first sexual experience) or **acquired** after months or years of satisfying sexual intercourses. To ask the woman what in *her* opinion is causing the current FSD may offer useful insights into the etiology of the disorder, particularly when it is acquired [17].
d) The **level of distress**, that indicates a mild, moderate, or severe impact of the FSD on personal life [44]. Sexual distress should be distinguished from non-sexual distress and from depression. The degree of reported distress may have implications for the woman's motivation for therapy and for prognosis.

3.2. Women's sexual desire/interest disorder

Hypoactive Sexual Desire Disorder (HSDD) is the sexual dysfunction most frequently reported by women [42]. The complaint of low desire becomes a sexual *disorder* when it causes severe personal *distress* to the woman.

Epidemiology

Population data indicate a prevalence of low desire in 32% in women between 18 and 59 years of age [45]. A recent European survey on 2467 women, in France, UK, Germany and Italy, indicates that the percentage of women with low sexual desire is 19% in the age cohort from 20 to 49; 32% in the same age cohort, in women who experienced surgical menopause; 46% in postmenopausal women aged 50 to 70 with natural menopause and 48% in the same age cohort, after surgical menopause. The percentage of women *distressed* by their loss of desire, having a HSDD, was respectively 27% in fertile women and 28% after surgical menopause, in the age cohort 20 to 49; 11% in women with natural menopause and 14% in those with surgical menopause aged 50 to 70. The likelihood of HSDD increases with age, whilst the *distress* associated with the loss of desire is *inversely* correlated with age [51,52].

Etiology of HSDD

Surgical menopause, secondary to bilateral ovariectomy, has a specific damaging effect due to the loss of ovarian estrogens and androgens [53]. Ovaries contribute to more than 50% of total body androgens in the fertile age. An European survey on 1356 women indicated that women with surgical menopause had an OR of 1.4; CI=1.1,1.9 p=0.02 of having low desire. Surgically menopausal women were more likely to have HSDD than premenopausal or naturally menopausal women (OR=2.1; CI=1.4, 3.4, p=0.001) Women with HSDD were more likely to be dissatisfied with their sex life and their partner relationship than women with normal desire (p<0.001) [54].

L**eading biological aetiologies of HSDD** include not only **hormonal factors** (low testosterone, low estrogens, or high prolactin), but also **depression** and/or **comorbidity with major diseases**. Premature iatrogenic menopause is the most frequent cause of a biologically determined generalized loss of desire; the younger the woman, the higher the distress this loss causes to her [54,55].

Clinical diagnosis

When the clinical history suggests a possible biological etiology, clinicians should assess:

- **The patient's hormonal profile:** total and free testosterone, dehydroepiandrosterone sulphate (DHEAS), prolactin, 17β-estradiol, sex hormone binding globulin (SHBG), with a plasma sample on the third or fourth day from the beginning of the menses in fertile women; follicle-stimulating hormone (FSH) and all of the above, in perimenopausal women; and thyroid-stimulating hormone (TSH) when individually indicated;
- **The pelvic floor,** in all its components, with an accurate gynecological, sexological and/or physiatric examination, particularly when comorbidity with arousal, orgasm and/or sexual pain disorders is reported;
- **Iatrogenic factors** such as drugs [1,2] (antiandrogens, aromatase inhibitors, tamoxifen, hyperprolactinemic drugs such a sulpiride) or poor outcomes of genital surgery (such as episiotomy-episiorraphy; posterior colporraphy; radical surgery for cervical cancer); or outcomes of vaginal, bladder or anal radiotherapy, leading to pain and secondary loss of desire.

- **Addictions** (drugs, alcohol, smoke).
- **Inappropriate lifestyles,** including the chronic shortage of sleep leading to chronic stress.

The biological evaluation should always be integrated with appropriate questions on:

- **Psychosexual factors and affective states**, depression above all, with referral to a psychiatrist, a sex therapist or couples therapist for a comprehensive diagnosis and treatment if indicated [50];
- **Context dependent factors,** including couple dynamics, or substantial factors such as work-a holism, professional distress, poverty.
- **Partner sexual or general health problems,** contributing to a secondary loss of desire (in this case the partner is the "problem inducer" and the woman the "partner carrier") should be specifically investigated. When diagnosed, the partner should be referred to the uroandrologist, the endocrinologist or the family physician, according to the leading diagnosis of his sexual dysfunction.

Principles of therapy

There is no effective therapy without accurate and comprehensive diagnosis. This is especially true for FSD, given the high frequency of multifactorial etiology.

An **interdisciplinary team** is the most valuable resource for a patient-centered approach, both for diagnostic accuracy and tailored treatment. Key professional figures include medical sexologist, gynecologist, urologist, psychiatrist, endocrinologist, physiatrist, anethesiologist, neurologist, proctologist, dermatologist, psychotherapist (individual and couple), sexologist, and physiotherapist.

HSDD is usually multifactorial and requires an integrated multimodal approach. **Biological etiologies** should be addressed with special attention to hormonal contributors, specifically in menopausal women (surgical and natural menopause).Hormonal therapy (HT) addresses the multiple changes menopause induces on women's sexual response. Testosterone patches specifically address the HSDD secondary to surgical menopause. Recent studies suggest that it may be equally effective in natural menopause [56,57]. Genital and pelvic floor-related pathologies, contributing to genital arousal difficulties, dyspareunia and/or orgasmic problems, contributing to a secondary loss of sexual desire should be assessed and addressed. The psychosexual and/or relational components should be addressed by a competent psychiatrist or psychotherapist/sexologist. There should also be a referral to a uroandrologist for male sexual disorders, when indicated.

3.3. Arousal disorders

Central arousal disorders ("I do not feel mentally excited") are comorbid with loss of sexual desire and can only with difficulty be separated from it.

Genital arousal disorders, with their key subjective symptom, vaginal dryness, are increasingly reported with age.

Epidemiology

Genital arousal disorders are complained of by 19–20% of women in epidemiological surveys [45], increasing to 39–45% in postmenopausal sexually active patients [42,54].

Pathophysiology

Mental arousal may be triggered through different pathways: **biologically by androgens and estrogens**, psychologically by **motivational forces like intimacy needs**. With successful genital arousal, most women produce increased quantities of vaginal transudate; the neurotransmitter vasoactive intestinal peptide (VIP) stimulates this neurogenic transudate production, through the powerful activation of estrogens; the neurotransmitter nitric oxide (NO) stimulates the neurogenic congestion of the clitoral, vestibular bulb and corpora cavernosa, through the activation of testosterone [24].

The **reduction in vaginal lubrication** is one of the most common complaints of postmenopausal women. When the plasma estradiol concentration is below 50 pg/mL (the normal range in fertile women being 100–200 pg/mL) **vaginal dryness** is increasingly reported [58]. Physiological studies indicate that after the menopause the vaginal pH increases from 3.5–4.5 to 6.0- 7.39 owing to decreased glycogen production and metabolism to lactic acid, with dramatic modification of the vaginal ecosystem, and an average reduction of vaginal secretions of 50%.

Etiology

Leading biological etiologies of arousal disorders include **loss of sexual hormones (in comorbidity with desire disorders)**, primarily estrogen, and **pelvic floor disorders**:

a) **Hyperactivity of the pelvic floor** may reduce the introital opening causing dyspareunia. Pain is indeed the strongest reflex inhibitor of genital arousal: genital arousal disorders, and the consequent vaginal dryness, are often co-morbid with dyspareunia [40,43]. Psychosexual and relational factors may also concur in this disorder;
b) A **hypoactive or damaged pelvic floor** (after traumatic deliveries, with macrosomic children or vacuum or forceps extraction) may contribute to genital arousal disorder because it reduces the pleasurable sensations the woman (and the partner) feel during intercourse [40].

Clinical approach

When a patient complains of an arousal disorder, the clinician should check if the disorder is mental ("I do not feel mentally excited"); genital ("I have vaginal dryness"; "It takes ages to get lubricated /wet") or mixed ("I do not get excited") [11].

Biological contributors to the complaint that should be checked include:

- **The hormonal profile**, more so in hypoestrogenic conditions such as long lasting secondary amenorrhea, puerperium, menopause, specially iatrogenic.
- **General health conditions.**
- **Pelvic health**, focusing on pelvic floor trophism: vaginal, clitoral, vulvar, connective and muscular (looking for both hypertonic and hypotonic pelvic floor dysfunctions) [40,43].
- **The vaginal pH** with a simple stick as vaginal acidity well correlates with estrogenic tissue levels and the vaginal ecosystem [40].
- Other **biological factors,** such as vulvar vestibulitis, or poor outcomes of perineal/genital surgery, causing introital and/or pelvic pain.

- **Vascular factors** that may impair the genital arousal response (smoking, hypercholesterolemia, atherosclerosis, hypertension, diabetes) [59].
- **Relational issues**, inhibition and/or erotic illiteracy, if a poor quality of mental arousal, poor or absent foreplay are reported [50].

Principles of therapy

Arousal disorders are usually multifactorial in etiology, often comorbidly occurring with HSDD. They require an integrated multimodal approach. Biological etiologies should be addressed with special attention to hormonal contributors, specifically in menopausal women (surgical and natural menopause).

Hormonal therapy

There is solid evidence that hormonal factors are involved in the genesis of FSD, so that their treatment is based on pharmacologic hormones. Indeed, during a woman's entire reproductive lifespan, sex hormones exert both organizational and activational effects on sexual behavior. Sexual hormones may be delivered by very different routes of administration: oral, transdermal, and nasal, vaginal, through subcutaneous implants or intrauterine devices. The most important difference between the oral route and those that bypass the first hepatic pass is that the oral treatment induces an increase of sex hormone-binding globulin (SHBG) by as much as 133%, thus significantly reducing free testosterone. Levels of SHBG seem to be unaffected by hormones delivered via transdermal, nasal, and vaginal routes.

Hormonal therapy addresses the multiple changes menopause induces on women's sexual response. Testosterone patches specifically address the HSDD secondary to surgical menopause, but has proven to significantly improve all the other dimensions of women's sexual response (arousal, orgasm, body image, while reducing the distress associated to FSD). Vaginal estradiol is indicated when the women complains specifically of vaginal dryness (ie "genital arousal disorder") but the does not want systemic treatments and/or they are contraindicated. Topical testosterone (2% testosterone propionate in petrolatum) has been anecdotally reported to improve clitoral arousal. However controlled studies are lacking in the Author's knowledge. Recent studies suggest that it may be equally effective in natural menopause [57]. Genital and pelvic floor-related pathologies, contributing to genital arousal difficulties, dyspareunia and/or orgasmic problems, contributing to a secondary loss of sexual desire should be assessed and addressed. Specifically, the role of a well trained physiotherapist is crucial to address the hyperactive or hypoactive pelvic floor and its role as a contributor of genital arousal disorders [46].

The **psychosexual and/or relational components** should be addressed by a competent psychiatrist or psychotherapist/sexologist.
A referral to **uroandrologis**t for male sexual disorders should be considered.

3.4. Orgasmic disorders

Orgasmic disorder has been reported in an average of 24% of women during their fertile years [45]. After the menopause, 39% of women complain of orgasmic difficulties, with 20% complaining that their clitoris 'is dead' [60] Orgasm is a sensorimotor reflex that may be triggered by a number of physical and mental stimuli [61].

Pathophysiology

Genital orgasm requires

- Integrity of the pudendal sensory nerve fibers (S2, S3, S4) and corticomedullary fibers.
- Cavernosal structures that, engorged and adequately stimulated, convey pleasant sensory stimuli to the medullary center and the brain.
- Adequate motor response of the pelvic floor muscles.

Short medullary reflex may trigger muscular response, characterized by the involuntary contraction (three to eight times, in single or repetitive sequences) of the levator ani. The medullary reflex may be eased or blocked, respectively, by corticomedullary fibers that convey both **excitatory stimuli** when central arousal is maximal and inhibitory ones when arousal is poor. Performance anxiety may activate adrenergic input, which disrupts the arousal response. **Inhibitory fibres** are mostly serotonergic: this explains the inhibitory effects of selective serotonin reuptake inhibitors (SSRIs) on orgasm in both men and women [62]. Fear of leaking during intercourse may inhibit coital intimacy and/or orgasm: leakage during coital thrusting is usually associated with stress incontinence, while leakage at orgasm is associated with urge incontinence.

Significant age-associated changes in the content of smooth muscle and connective tissue in the clitoral cavernosa, contributing to age-associated clitoral sexual dysfunction, causing hypo-anorgasmia, have been demonstrated from the first to the sixth decade of life [63].

Clinical approach

Using the information emerging from the clinical history as a starting point, the physician should look for:

- Hormonal balance.
- Signs and symptoms of vulvar dystrophy and, specifically, of clitoral and vaginal involution [41].
- Traumatic consequences of female genital mutilation (infibulations).
- Signs and symptoms of urge, stress or mixed incontinence, either of a hypotonic or hypertonic pelvic floor [62].
- Iatrogenic influences when potentially orgasm-inhibiting drugs are prescribed, or when pelvic surgery and/or radiotherapy have disrupted the nervous/vascular/muscular components contributing to the orgasmic reflex.

Principles of therapy

Biological factors should be treated with a strategic approach, addressing potential hormonal (see HSDD and arousal disorders), pelvic floor related (see arousal disorders) and iatrogenic issues, with special attention to the inhibiting effects of SSRI and/or tricyclic antidepressant. Bupropion should be the drug of choice, if the orgasmic disorders appear to be caused specifically by the antidepressant drug the patient is using.
Psychodynamic/sexual issues should be treated as indicated above.

3.5. Sexual pain disorders

Various degrees of **dyspareunia** are reported by 15% of coitally active women, and 22.5–33% of postmenopausal women. **Vaginismus** occurs in 0.5–1% of fertile women. However, mild hyperactivity of the pelvic floor, that could coincide with grade I or II of vaginismus may permit intercourse causing, though, coital pain [64].

Pathophysiology

Vaginal receptiveness is a prerequisite for intercourse, and requires anatomical and functional tissue integrity, both in resting and aroused states. Normal trophism, both mucosal and cutaneous, adequate hormonal impregnation, lack of inflammation, particularly at the introitus, normal tonicity of the perivaginal muscles, vascular, connective and neurological integrity and normal immune response are all considered necessary to guarantee vaginal 'habitability' and sexual responsiveness. Vaginal receptiveness may be further modulated by psychosexual, mental and interpersonal factors, all of which may result in poor arousal with vaginal dryness [65].

Fear of penetration, and a **general muscular arousal secondary to anxiety**, may cause a defensive contraction of the perivaginal muscles, leading to vaginismus [66]. This disorder may also be the clinical correlate of a **primary neurodystonia of the pelvic floor**, as recently proven with needle electromyography [41]. It may be so severe as to prevent penetration completely. The defensive pelvic floor contraction may also be secondary to genital pain, anal or bladder pain, of whatever cause.

Etiology

Dyspareunia is the common symptom of a variety of coital pain-causing disorders (**Box 2**). **Vulvar vestibulitis** is its leading cause in fertile age. The diagnostic triad is: 1) severe pain upon vestibular touch or attempted vaginal entry; 2) exquisite tenderness to cotton-swab palpation of the introital area (mostly at 5 and 7, when looking at the introitus as a clock face); 3) dyspareunia. The reader is referred to other publications for a more detailed analysis of different etiologies of coital pain. [65,67].

Vaginismus is a painful spasm of pelvic floor muscles (levator ani) around the vagina. When mild, it makes intercourse painful, thus contributing to introital dyspareunia. Microabrasions secondary to the intercourse in dry conditions and with a tightened elevator ani, may contribute to a chronic vestibular inflammation leading to vulvar vestibulitis. When severe, it makes intercourse impossible: it is then the most frequent female cause of unconsummated marriage. It may express the local muscular correlate of a systemic muscular tension, secondary to a general systemic arousal due to the phobic attitude. Or it may be the expression of a local myogenic hyperactivity of the levator ani, isolated or secondary to genital, bladder or anal pain [65,67].

Pathophysiology

From the pathophysiologic point of view, vulvar vestibulitis involves the up-regulation of: a) the immunological system, ie of introital mast-cells (with hyperproduction of both inflammatory molecules and nerve growth factors (NGF) [10]; b) the pain system, with proliferation of local pain fibers induced by the NGF, which

contributes to neuropathic pain; c) hyperactivity of the levator ani, which can be antecedent to vulvar vestibulitis, or secondary to the introital pain.

Hyperactivity of the pelvic floor may be triggered as well by non-genital, non-sexual causes, such as urologic factors (urge incontinence, when tightening the pelvic floor may be secondary to the aim of reinforcing the ability to control the bladder), or anorectal problems (anismus, hemorrhoids, rhagads).

Box 2. Leading Biological etiologies/risk factors of Dyspareunia (introital/superficial and deep).

INTROITAL DYSPAREUNIA
Inflammatory, with or without infection C.D: vulvar vestibulitis, vulvitis, vaginitis, post-coital cystitis, interstitial cystitis
Hormonal C.D*:* vulval-vaginal atrophy/dystrophy, vaginal dryness
Muscular C.D.: pelvic floor myalgia, with tender and/or trigger points
Iatrogenic C.D: side effects of perineal surgery, genital radical surgery for cervical cancer or pelvic radiotherapy
Neurologic C.D.:neuropathic pain; or associated with a specific neurologic disease such as multiple sclerosis
Psychiatric CD: anxiety, depression
Gastrointestinal CD: ulcerative colitis, irritable bowel syndrome
Vascular CD: vaginal dryness (secondary to atherosclerosis, hypertension, diabetes)
Immunological CD: lichen sclerosus, Sjogren' syndrome
Anatomical CD: according to the physical finding, such as a rigid, fibrotic hymen
DEEP DYSPAREUNIA
Endometriosis CD:endometriosis; invalidating chronic dysmenorrhea and/or deep dyspareunia
Pelvic inflammatory disease (PID) CD: Sexually Transmitted Disease (STD); adnexitis;
Pelvic varicocele CD: echographic diagnosis of usually left varicocele
Iatrogenic CD : iatrogenic vaginal shortening/narrowing;
Neurologic CD: acute pain elicited in the site of previous surgical abdominal incision (ACNES Abdominal Cutaneous Nerve Entrapment Syndrome);
Referred abdominal pain CD: fibromyalgia; myalgic pelvic floor
Chronic pelvic pain CD: same

LEGEND: CD=Clinical Diagnosis
Adapted from Graziottin & Rovei [65]

Comorbidity with other sexual dysfunctions – loss of libido, arousal disorders, orgasmic difficulties, and/or sexual pain related disorders – is frequently reported with persisting/chronic dyspareunia.

Comorbidity between dyspareunia and other medical conditions is as well frequent and under-reported. For example, in the survey of Peters and coworkers, interstitial cystitis is associated with a significantly higher incidence of dyspareunia and fear of intercourse since the first intercourse, suggesting that the hyperactivity of the pelvic floor and sexual pain disorders are important contributors to the pathophysiology of bladder chronic inflammation and pain [68].

Clinical approach

The **diagnostic work-up** should focus on [65,67]:

- **Physical examination**: to define the 'pain map' (any site in the vulva, midvagina and deep vagina where pain can be elicited)**,** as location of pain and its characteristics are the strongest predictors of type of organicity; pelvic floor trophism (vaginal pH), muscular tonus, strength and performance, signs of inflammation (primarily vulvar vestibulitis), poor outcomes of pelvic or perineal surgery (primarily episiotomy/rraphy), associated urogenital and rectal pain syndromes, myogenic or neurogenic pain and vascular problems and assess biological common denominators (such as the hyperactive pelvic floor) of medical comorbidities;
- **Psychosexual factors**, poor arousal and coexisting vaginismus; comorbidity with other sexual dysfunctions; investigation of any potential previous traumatic sexual experiences.
- **Relationship issues**
- **Hormonal profile**, if clinically indicated when dyspareunia is associated with vaginal dryness.

4. Current status of medical therapy

This latter professional is emerging as a key resource in addressing pelvic floor disorders, which are finally receiving the attention they deserve as key biological factors in the etiology of FSD. Pain is rarely purely psychogenic, and dyspareunia is no exception. Like all pain syndromes, it usually has one or more biological etiologic factors. Hyperactive pelvic floor disorders are a constant feature. However, psychosexual and relationship factors, generally lifelong or acquired low libido because of the persisting pain, and lifelong or acquired arousal disorders due to the inhibitory effect of pain, should be addressed in parallel, in order to provide comprehensive, integrated and effective treatment.

In tailoring of treatment, the physiotherapist has a crucial role, especially in sexual pain disorders, either lifelong or acquired, and in acquired desire, arousal or orgasmic disorders secondary to coital pain. A multimodal, individually tailored treatment (pharmacologic, physiotherapic, behavioural, psychodynamic, antalgic) is currently used for both dyspareunia and vaginismus.

4.1. Practical tips

Key points in the FSD diagnosis, preliminary to a well tailored treatment, should be:

a) **Accurate listening to the complaint's wording**, to verbal and non verbal messages, with:

- Definition of the nature of the disorders.
- Its being lifelong or acquired.
- Generalized or situational.
- Organic, psychogenic, contextual or, as it is in most cases, mixed, with definition of key predisposing, precipitating and maintaining factors;
- The severity of the distress the FSD may cause.
- The sexual and/or medical (urogenital, proctological etc) associated comorbidity.
- Partner's related issues.
- The personal motivation the woman has (or does not have) to treatment of FSD, which includes the meaning of the symptom for the woman.

b) **Accurate examination of the woman**, and particularly of the external genitalia, of the vagina and of the pelvic floor. Careful physical examination should be performed, as the biological etiology of FSD is better diagnosed when attention is paid to:

- Vulvovaginal trophism with pH recording.
- Hypo or hypertonic pelvic floor conditions, with tender and trigger points evaluation.
- Inflammation and infections' diagnosis, with coltural exams when indicated.
- The pain-map accurate description as location of pain and its onset characteristics are the strongest predictors of its biological etiology.

4.2. Key points for treatment

The delay in the medical approach to FSD, and the persistent psychological perspective, still make it difficult to have evidence-based medical treatments of FSD, except in the domain of sexual hormones. The testosterone patch, approved by the EMEA (European Medicine Agency) in July 2006, is the only drug currently approved with the specific indication of HSDD in surgically menopausal women. As a result of diagnostic delays, inadequacies, and gender biases, **no other treatment for FSD is currently approved with this specific indication**, with the exception of a clitoral device indicated for female arousal disorders.

Next section will briefly consider the pharmacologic scenario that potentially may be used in the medical treatment of FSD in the future.

5. The future of medical treatment

This section will discuss treatments currently used for FSD, which have a high probability of continued use in the future, along with a better understanding of their therapeutic role. In addition, new treatments which are currently being actively investigated will also be explored.

5.1. Hormonal treatments

Sexual hormones are critical contributors of women's sexuality, through their complex mechanisms of action on the brain, on the genitals and the different key

systems (vascular, nervous, endocrine, muscular, immunitary, metabolic) contributing to sexual function. Furthermore, hormones influence synthesis, storage and release of brain neurotransmitters. They substantially modulate **neuroplasticity**, ie the ability of neurons to continuously adapt to inner and external stimuli by rearranging their intense intercommunicating network through the dynamic reshaping of the dentritic tree and of the continuous remodeling of the dentric spines. These structures are really the morphologic correlate of **psychoplasticity**, ie the biologic background that support the extraordinary adaptability, flexibility and creativity of the human brain [12]. Sexual hormones improve the ability of neurons and cerebral vessels to repair the damage secondary to internal or environmental toxic stimuli and to cope with the aging process. Recent data from Walter Rocca and coworkers [69] showed increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause, have substantiated the very negative impact on the brain of monolateral or bilateral oophorectomy, leading to significantly increased risk of cognitive impairment or dementia (OR=1.46) and of parkinsonism (OR=1.68) [70]. A functional brain is a prerequisite for the integrity of cognitive, motor, affective and neurovegetative functions, including sexual function.

Loss of sexual hormones may as well contribute to disrupt the hormone-dependent biological basis of sexual function. It may be spontaneously reversible, in conditions such as hypothalamic amenorrhea and post-partum amenorrhea, when the woman is lactating. It is irreversible, by definition, after the menopause, with a more sudden drop of sexual hormones' levels after surgical bilateral oophorectomy, leading to surgical menopause.

Menopause is characterized by the exhaustion of the ovarian production of oocytes, estrogens and progesterone, with consequent permanent amenorrhea, anovulation and sterility. The ovarian production of testosterone is gradually reduced from the twenties onwards, but is maintained across natural menopause [71,72]. It is completely lost in surgical menopause (bilateral oophorectomy). The loss of sexual hormones has a widespread effect on all systems and organs, as virtually all cells of the female body have receptors for sexual hormones [73]. This loss accelerates the negative multi-systemic effects of ageing, with a further detrimental effect, which affects sexuality in a complex way. Epidemiological studies indicate that current key predictors of HT use are: *age at menopause* (the younger the women the higher the probability she will require and be prescribed HT); *type of menopause* (surgical menopause is three times more likely to be hormonally treated) and *education and socioeconomic level* (women better educated and with higher socioeconomic background are more likely to require and use HT) (reviewed in [74]). This trend is likely to be maintained in the future, even when Ht is indicated to relieve sexual symptoms. Unfortunately, the Women's Health Initiative (WHI) publication [75] and the following data analysis [76,77] led to concerns, fear and distrust toward HRT, in women and in physicians [74]. WHI data exacerbated the worries previously raised by the Heart and Estrogen/Progestin Replacement Study (HERS I) [78] and HERS II [79]. The Million Women Study (MWS) [80], in spite of its lower level of evidence (II-2) compared to the WHI (I) and HERS I and HRS II (I), further increased concerns by the extensive negative media coverage it generated. Weaknesses and strength of the WHI have been discussed in previous papers [74,81-86].

Box 3. Contraindications to hormonal therapy after the menopause.

- Current, past or suspected breast cancer
- Known or suspected estrogen-dependent genital malignant tumors (e.g. adenocarcinoma of the endometrium, ovary and cervix)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary thromboembolism)
- Active or recent arterial disease (eg. angina, myocardial infarction)
- Untreated hypertension
- Active liver disease (hepatitis)
- Chronic cholangitis
- Porphyria cutanea tarda (an absolute contraindication)
- Known hypersensitivity to the active substances or to any of the excipients

Modified from [67].

An extensive re-reading of WHI data is on the way, with the emergence of the concept of "critical time window" or "window of opportunity". The concept of "*window of opportunity*" [83] suggests that *timing of HT* may be critical in modulating positive or adverse effects **(Box 3)**. When the appropriate, well tailored, hormonal replacement therapy (HRT), according to the Europeans, or replacement therapy (HT), according to North-americans, is initiated during or soon after the menopause, is likely to carry much more benefits than risks to the individual women. With increasing age, risks related to a late initiation of HT are increasingly likely to outweight the benefits.

HT is still and will likely be the cornerstone of a well designed treatment to maintain an optimal sexual function after the menopause, more so when it is premature. The sooner the treatment is initiated, the better. The complex impact of HT on the brain and its multiple systems (neurovegetative, affective, cognitive and motor), on the peripheral nervous system and on the vessels is a prerequisite to maintain an optimal biological component of desire, arousal (central, peripheral-non genital and genital) and orgasm. The potential of different hormonal treatment will be further documented in prospective studies.

The future will increasingly elucidate the critical role of sexual hormones as a necessary – although not a sufficient condition – to maintain a satisfying working brain, in spite of aging. Hopefully they will as well substantiate their synergistic role with neurotransmitters and other neuroactive drugs in maintaining the biological prerequisites of a satisying sexual function in women after the menopause, either natural or iatrogenic.

Key aspects of hormonal therapy

HT consists of an estrogen (estradiol or equine conjugated estrogens) combined with a progestogen, in non-hysterectomized women. Progestogens are given either cyclically or continuously with the estrogen, to protect the endometrium from hyperplasia. They are not indicated in hysterectomized women. Different routes of administration are used: oral, transdermal, subcutaneous, intranasal and vaginal. Because of the lack of the

first-pass effect on the liver, the non-oral route of administration may be preferable in women with hypertriglyceridemia, migraine headache or even increased risk of venous thrombosis [83]. Progestogens can be administered through an intrauterine device (IUD). Over 50 types and combinations of HT are available [85].

Systemic hormonal treatment

Estrogens and progestins

Pros and cons of hormonal treatment with estradiol and progesterone or progestins on women's sexuality are reviewed in [82-84]. HT is credited to relieve sexual symptoms, with a domino positive effect on sexuality in general, but not a specific effect on libido, unless progestins with a specific androgenic effect, like norethisterone, are used.

Tibolone

It is a derivative of norethynodrel, a progestogen with androgenic activity. It has been defined as a selective tissue estrogenic activity regulator (STEAR). Tibolone is a prodrug that rapidly converts after intake in the intestinal tract and liver to various metabolites that are systemically active as progestogen, androgen or estrogen. It has different actions on different target organs, which provide an overall favorable risk-benefit profile [40,83,87,88]. Clinically, tibolone treats menopausal symptoms, including hot flushes and vaginal dryness, as effectively as estrogen therapy, and, most importantly, improves sexual response, while having a positive effect on the bone [83,87]. Widely used across the world, it is not approved in the USA, at the time this paper was written (April 2008).

The future: HT with estradiol and noretistherone and tibolone is currently credited to offer the best impact on women's sexuality, besides the improvement of menopausal symptoms. These products are widely used and are likely to maintain a solid position in the future of medical treatment of FSD, as modulators of the women's general and sexual health.

Testosterone

It is currently the only drug specifically approved to treat Hypoactive Sexual Desire Disorder (HSDD) in surgically menopausal women. RCT indicate the positive effect of androgens, namely testosterone, on different domains of female sexual function: desire, arousal orgasm, body image, with reduction of anxiety and distress [reviewed in 42 and 89]. The data from the Phase III studies, known as the Investigation of Natural Testosterone in Menopausal women Also Taking Estrogen in Surgically Menopausal women (INTIMATE SM) 1 and 2 showed a significant increase in total satisfying sexual activity, in those women receiving testosterone, compared with those women in the placebo group. Total satisfying sexual activity increased by 74% and 51% for INTIMATE 1 and 2, respectively. The Profile of Female Sexual Function instrument demonstrated significant improvements in INTIMATE 1 and 2 in all domains of sexual function in testosterone-treated women compared with the placebo patients. In both studies, personal distress decreased in those patients receiving testosterone, compared with the placebo group. The most commonly reported adverse events were application site reactions. Eight-five percent of patients said they would probably or definitely continue treatment. The transdermal testosterone patch is an effective treatment for

hypoactive sexual desire disorder in surgically postmenopausal women receiving concomitant estrogen therapy. The treatment has a favorable safety profile [90].

Despite these results, the classification of reduced androgen as a medical syndrome remains controversial. A task force of the Endocrine Society recently published treatment guidelines regarding androgen therapy in women [91]. The task force recommended against making a diagnosis of androgen deficiency in women, due to the lack of a well-defined clinical syndrome and normative data on total or free testosterone levels across the lifespan that can be used to define the disorder. Although the task force acknowledged that clinical trial data show short-term efficacy of testosterone replacement in surgically postmenopausal women, they recommended against the generalized use of testosterone by women because of the lack of clear definitions of indications concerns over long-term safety. A response questioning the wisdom of these guidelines from the sexual medicine community has been signed by most credited experts in the field of sexual medicine [92]. In summary, there is considerable support recognizing the importance of maintaining adequate androgen levels for good sexual response, but there is inadequate data to support prescribing androgen supplementation as a panacea for desire, arousal and/orgasm disorders in women [93,94].

The future: Testosterone patch is currently used in Europe, where it was approved by EMEA (European Medicine Agency) in July 2006. It will be a cornerstone of medical therapy of HSDD and associated FSD in the future, if the whole spectrum of benefits for the women's health and specifically for the brain will be appreciated by physicians and women alike.

Genital hormonal treatments

Vaginal estrogens

Atrophic changes in the urogenital tract and their consequences (e.g vaginal dryness, dyspareunia, urinary frequency and urgency, post-coital cystitis) are improved by estrogen therapy (ET). When prescribed *solely* for the treatment of such symptoms, topical low dose vaginal products are the treatment of choice [55,74,95,82-84]. ET may well address the urogenital comorbidity [96] that increases with increasing age, unless appropriate ET is prescribed. Long-term treatment is often required as symptoms can recur on cessation of therapy. Every systemic and local ET/EPT product is government-approved for this indication [81].

Vulvar testosterone

Topical testosterone (2% testosterone propionate in pretrolatum or vaseline jelly) anecdotally improves clitoral congestion, reduces the lag time between onset of vulvar stimulation and orgasm, and facilitates more intense orgasms. However, controlled studies are still lacking in Author's knowledge.

The future: Given the efficacy and the excellent profile of safety, vaginal treatments with estradiol or other estrogens are very likely to be used in the future for the cure of genital arousal disorders (contributing to vaginal dryness), dyspareunia, post-coital cystitis. Controlled studies could substantiate the positive effect of topical testosterone emerging in the clinical practice. These two treatments could well be used in the future sexual medicine for their safety, efficacy, easiness of use and acceptability by women, given their topical, cutaneous route of administration with reduced or marginal systemic effects.

5.2. Non hormonal systemic drugs

Central nervous system acting drugs

The role of the CNS in women's sexuality is evident, but has remained under-researched [4]. Critical aspects include a better understanding of contributions to sexual response of the neuroanatomical, neuroendocrine, and neurochemical systems, including the inter-related role of sex steroids and neurotransmitters in the CNS and periphery. Neurotransmitters modulate the secretion of many hormones (eg, gonadotropin-releasing hormone, luteinizing hormone, testosterone, prolactin and endorphins) involved in sexual functional capacity. Potential differences between sexually functional and dysfunctional women in dopamine (DA) and norepinephrine (NE) responses to erotic stimuli were recently investigated [97]. Blood levels of homovanillic acid (HVA; the major metabolite of DA) and NE were taken during the showing of a nonsexual and a sexual film from 9 women with female sexual arousal disorder and hypoactive sexual desire disorder and from 13 sexually functional women. Sexual arousal was assessed subjectively using a self-report scale and physiologically using a vaginal photoplethysmograph. HVA levels significantly decreased in sexually functional and dysfunctional women during the erotic versus during the neutral film. NE levels were not significantly different for either group of women during the neutral and erotic films. Sexually dysfunctional women had significantly higher levels of NE during both the neutral and erotic films compared with functional women.

Functional magnetic resonance imaging (fMRI) of the brain is providing new insights into the role of the CNS in human sexual response [98-101]. In healthy young women shown an erotic film, neocortical areas of the brain were activated, along with parts of the limbic system, including the parahippocampal gyrus, septal area, cingulated gyrus and hypothalamic area [98]. At orgasm, a number of brain centers are activated, including areas in the hippocampus, hypothalamus, basal ganglia, cerebellum, the parietal and frontal cortices, and the lower brain stem [101]. Other investigations of brain activation have shown that the brain responds differently to estrogen therapy depending on age and menstrual status, thus suppporting the critical role of sexual hormones in modulating brain functioning, with a more evident action on levels of neurotranmitters [102].

Key neurotrasmitters in women's sexual function

Dopamine

It is the key mediator of the seeking-appetitive system, whilst opiates mediate the lust system, associated with it. The seeking-appetitive-lust system modulates all the environment-related behaviours directly or indirectly connected with survival linked to reproduction. According to Jaak Pankseep, it is one of the four basic emotion command systems (the other being the anger-rage, the fear-anxiety and the panic with separation distress). Dopamine mediates seeking food, water, shelter, sex, dominance (if the animal lives in group), the level of vital energy, the assertiveness and overall a proactive approach (reproductive and non reproductive) to life. Drugs which influence dopamine are likely to play a key future role in sexual medicine.

Serotonin

Serotonin has a specific role in suppressing the sexual response for both men and women. Effects of SSRIs on sexual functioning seem to be dose-related based on the

relative impact of individual agents on both the serotonin and dopaminergic systems [103]. The mechanism for this effect appears to be related to the interaction between serotonin and dopamine. Elevated CNS levels of serotonin impacts on dopamine transport, which could be functionally linked to an overall decrease in dopamine neurotransmission, and more-efficient removal of the dopamine from the synaptic regions [104]. In males, increased serotonin levels have been recognized to cause retrograde or delayed ejaculation and that observation provided much of the scientific rational for using SSRI's to treat premature ejaculation [105, 106].

Drugs with a future in the medical treatment of FSD

The relatively inhibiting effect of serotonin on sexual functioning is also reflected by the much-reported observation that female patients being treated with SSRIs for depression were experiencing diminished sexual response [103].

Bupropion

It is an antidepressant with a peculiar effect of sexual function. There is some evidence that bupropion does not share the inhibitory effect other SSRI have on sexual function [107-109]. **Bupropion** may have different impact on dopamine transport than other antidepressants [104]. In addition, some studies have shown that bupropion can have a beneficial effect on sexual dysfunction commonly reported in patients receiving SSRIs for treatment depression [110, 111]; although not all studies have been positive in this regard [112]. In addition, the usefulness of bupropion in sexual dysfunction not caused by SSRI medical therapy is still an open question. Perhaps the most beneficial use of bupropion is one of augmentation. Bupropion supplementation may assist in maintaining an antidepressant benefit for the patient, as an offending SSRI is reduced in dosage, so that a better balance can be obtained between elevating mood and minimizing the anti-sexual side effects. Other agents with CNS mechanisms of action, including granisetron and ginko balboa, have not proven effective in clinical trials [113].

Flibanserin

Flibanserin is a post-synaptic 5-HT1A agonist, a very weak partial agonist on dopamine D(4) and a 5-HT2A antagonist [114, 115]. Interest for this molecule increased in the late nineties, when scientists were looking for an antidepressant with a rapid onset of action. Indeed, one of the still unmet needs in the treatment of depression is the availability of antidepressants that do not need repeated administration to get their biological and behavioural effect [116].

The background: current antidepressants exert an acute effect at the presynaptic level. Almost all block the uptake of monoamines or inhibit the acrivity of the enzyme monoamine oxidase, more or less selectively. However, the therapeutic effect of the current antidepressants is achieved only after repeated administration. The net effect of the antidepressant is credited to be the increase of monoamine concentrations in the synaptic cleft and, consequently, to induce changes in those receptors upon which a particular monoamine acts. There phenomena need time for induction [116].

Recently a new potential therapeutic combination has been proposed in which a serotonin (5-HT9 uptake blocker is administered together with pindolol, an antagonist of

the presynaptic dendrosomatic 5-HT 1A receptor. This combination allows achievement of an increased 5-HT synaptic concentration in the cortex within a shorter period of time.

Acting at post-synaptic receptor level a drug could mimic the effects exerted by long term antidepressant treatments, thus avoiding the delay due to adaptation of pre/post synaptic mechanisms. Moreover, several lines of evidence indicate the frontal cortex as a possible target for the therapeutic effect of antidepressants or as an important area for the occurrence of depression.

Given the high co-morbidity between depression and HSDD, an antidepressant with a specific action on the prefrontal cortex (besides hippocampus and midbrain) could present new potentials also on the front of HSDD.

Flibanserin seems to satisfy the need of a short acting drug, working at post-synaptic level as 5-HT1A agonist, a very weak partial agonist on dopamine D(4) and a 5-HT2A antagonist.

Flibanserin is currently under development for Hypoactive Sexual Desire Disorders (HSDD) and female central sexual arousal disorders [114]. No clinical trial data have been published to date. However, a number of large clinical studies are ongoing, which are anticipated to recruit more than 5,000 premenopausal women with hypoactive sexual desire disorder. Some of these studies anticipate reporting results mid-2008 [117].

The future: Flibanserin is currently the first direct post-synaptic 5-HT 1A receptor agonist, with an effect within a very short period of time. This short lag time between intake and clinical benefit would make is suitable for a sexual indication, were the positive action on desire supported by prospective studies. Its non hormonal status would make it a preferred choice for women with HSDD who do not like to use hormones to improve their sexual desire, and/or who cannot use them (as breast cancer patient). It could also be an opportunity for women who use hormonal contraception but complain of low desire because of it and, in general, for overstressed or depressed women in the fertile age who would like to maintain a better desire and sexual life.

Bremelanotide

Bremelanotide is a synthetic melanocortin analog of a melanocyte-stimulating hormone, and is an agonist at melanocortin receptors MC3R and MC4R [118]. The melanocortin system has been discovered to have properties that impact on human sexual behaviour. Much like the serotonergic system, the melanocortins have both inhibitory and excitatory properties, depending on the site of their activity at various receptors and subreceptors. Melanotanin II and its analogue bremelanotide were directly erectogenic in males and were facilitative of sexual receptivity and/or proceptivity in females. Early clinical evidence strongly suggested that bremelanotide might have an erectogenic effect in males [119]. Early clinical evidence has also emerged regarding the efficacy of bremelanotide for females. The primary adverse effects associated with bremelanotide were nausea, headache and nasal congestion. There may be potential for dose reduction to improve the adverse event profile while maintaining good efficacy outcomes. A Phase 2 study was scheduled to explore this hypothesis with bremelanotide as a take-home medication. However, at this time it seems more likely that future research will explore other similar peptides which maintain the pro-sexual effects of bremelanotide, but have only a fraction of the blood pressure activity.

The lack of consistently reproducible results with various forms of medical therapy probably argues for a more comprehensive approach to FSD than the "one size fits all" solution that has characterized the male erectile dysfunction treatments to date. It has been suggested that the contextual sensitivity of female sexual response may even more frequently require the use of a combination treatment, where sexual pharmaceuticals and sex coaching is integrated more frequently for women than it has been for men [120]. For some of these patients, a pharmaceutical monotherapy will be adequate to biologically trigger the cascade of changes needed for a satisfactory sexual response to occur. These types of situations account for the successes experiences with the earlier varieties of monotherapy discussed in this chapter, whether vascular, hormonal, or as the secondary benefit of a centrally acting antidepressant. The more specific and concrete the cause of the FSD, the more specific and concrete the treatment may be that alleviates the problem. Newer centrally acting agents will likely benefit some in a similar manner. However, the greatest utility of a CNS-acting agent might be found in assisting a patient to open up to higher levels of desire and/or arousal within the context of strategic use of other complementary forms of therapy. The future of sexual medicine and the treatment of FSD in particular may be aided mostly when centrally acting compounds which enhance sexual response are combined with hormonal supplementation, vasocongestive agents, and sexual counseling in a manner individualized to the needs of the patients. Such a multifaceted approach would certainly result in an exciting new era for sexual medicine and the treatment of various forms of female sexual disorders [120].

The future: CNS-acting drugs could represent a revolution in the treatment of HSDD in women, if their efficacy and their safety will be confirmed. They could become the drugs of choice for women suffering from HSDD and central arousal disorders who cannot or would not use hormones, and/or who do not have any improvement from the traditional hormonal therapies.

5.3. Non hormonal peripherally acting treatments

Vasoactive agents in women

There is no doubt that the development of PDE-5 inhibitor therapy for male erectile dysfunction revolutionized the treatment of sexual dysfunction [121]. Preclinical work with clitoral tissue baths suggested a rationale for use of these agents in female dysfunction [122]. However, clinical investigations into vasocongestive therapies for FSD have yielded inconsistent results. Research to date regarding use of PDE-5 inhibitors in women has not shown consistent evidence that this approach is effective [123, 124]. Attempts to gain a regulatory indication of sildenafil for female sexual dysfunction seem to have been abandoned, and it does not currently appear that the other competitors in the market have any interest in pursuing this line of clinical research [125].

The future: Vasoactive agents could nevertheless have a role for the subset of women with biologically determined genital arousal disorders (for example after genital/pelvic radiotherapy with local vascular damage) in combination with centrally acting drugs to promote sexual desire if HSDD in present in co-morbidity.

Botulin toxin

Since the late 1970s botulinum toxin (BoT) has been introduced as a therapeutic tool. Among other conditions, dystonia, spasticity, autonomic disorders including hyperhidrosis,

gastrointestinal tract dysfunctions are currently managed with BoT. BoT reduces muscular activity by inducing a presynaptic block of the cholinergic synapse, and reduces local pain probably by decreasing the release of substance P. Because the adverse effects are very rare and transient, BoT is well tolerated.

More recently this therapy has been employed for pelvic floor disorders, including pelvic muscle spasms, chronic pain syndromes, and genitourinary disturbances. [126] In the past vaginismus was considered a typical "psychogenic" disorder, treated with a psychosexual/psychodynamic approach. Later a sexo-behavioral treatment was considered more appropriate. More recently SSRI and anxiolytic have been proposed to reduce the systemic phobic arousal and anxiety associated with the disorder. Physiotherapy has been used to work more effectively on the pelvic floor. This multimodal treatment has proven successful in a variable percentage of cases, between 72 and 85%.

A subset of patient with severe phobic attitude and a tightened pelvic floor with a myogenic component do not respond to the current multimodal treatment. For these patients no effective treatment was available before BoT. BoT injected under electromyographic (EMG) guidance in pelvic floor muscles (levator ani or outer third vagina muscles) improves patients with vaginismus, addressing the specific myogenic hyperactivity of the levator ani. Integrated with a multimodal treatment (pharmacologic with SSRI and benzodiazepines, pelvic floor physiotherapy, and a short psychosexul treatment) it contributes to restore the possibility of intercourse leading to a more complete sexual life. BNT injections also improve the pelvic floor hyperactivity associated to vestibulodynia and vulvar vestibulitis. Though sometimes periodic injections are needed, the benefit is permanent in approximately 60% of affected women. [127, 128].

Urinary dysfunctions due to inflammatory central nervous system diseases can also take advantage of BoNT administration.

The future: Controlled studies will better indicate the role of BoT in the multimodal treatment of severe vaginismus, dyspareunia and related medical co- morbidities secondary to the myogenic hyperactivity of the pelvic floor.

Conclusions

Approaches to FSD treatment have ranged from psychological counselling through a variety of medical interventions along the physiological pathways of sexual function and dysfunction. Despite a great deal of research, especially into hormonal and vasoactive substances, little therapeutics has broad consistent applicability and has withstood scientific scrutiny.

Fortunately, the pharmacologic treatment of FSD is now facing a new era. Hormonal treatments, currently used to treat menopausal symptoms, will hopefully be considered to improve sexuality as a critical part of a rewarding quality of life and aging. Testosterone patches, currently the first drug for FSD to be marketed in Europe with the indication of HSDD in surgically menopausal women, should be considered with broader indications, such as HSDD in natural menopause or iatrogenic menopause other than surgery (i.e chemotherapic or radiotherapic).

Moreover, recent clinical trials have investigated the potential role of agents which act on the central nervous system (CNS) for the treatment of FSD. Bremelanotide and flibanserin are currently the most studied. They could cover the area on younger women with HSDD who cannot ot would not take hormones to improve their desire and sexuality.

While the recent data supporting the therapeutic use of centrally acting agents, as a monotherapy for FSD is cautiously encouraging, there would seem to be tremendous promise for these centrally acting compounds to be integrated with treatment approaches that utilize other pathways in a multi-layered, individualised approach to care.

In parallel to this spring in the scientific research, there should a parallel growth in physicians' attitude to take care of FSD in the clinical setting. The goal is to give women and couple the full potential of a joyful sexuality in their life-span.

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