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Medical treatment for sexual problems in women

Alessandra Graziottin, MD* - Audrey Serafini MD**

* Director, Center of Gynecology and Medical Sexology, H. San Raffaele Resnati, Milan, Italy

Consultant Professor, University of Florence, Italy

President and Founder, the Graziottin Foundation for the cure and care of pain in women

** Specialty School, San Raffaele Hospital, Milan, Italy

Introduction

Cancer today is more of a chronic than a fatal disease: the improving survival rates increase the likelihood of long survival after the diagnosis. Unfortunately, cancer treatment is the most frequent cause of premature iatrogenic menopause and psycho-sexual dysfunction. Therefore, an increasing number of cancer survivors have to cope with both the consequences of cancer treatment per se, the complex physical and psychological changes secondary to a premature iatrogenic menopause, and the burden of sexual dysfunctions, more difficult to accept in the youngest patients. Female sexual identity may be variably affected by a cancer diagnosis and treatment depending on the age at diagnosis (and the age at the time of any recurrences). Age is the first biological factor that may modify the outcome of cancer diagnosis and treatment, when sexuality is considered as an independent variable in the QOL evaluation. The impact of cancer is increasingly worse in younger patients, especially if radical surgery, adjuvant systemic chemotherapy and/or local radiotherapy further reduce the biological chances of a fulfilling sexual and procreative life.

Iatrogenic Menopause

Iatrogenic menopause defines the appearance of menopause as a consequence of medical treatment, for benign or malignant conditions. In cancer patients, it may be the consequence of surgery (bilateral ovariectomy), chemotherapy and/or radiotherapy.

Irreversible iatrogenic ovarian damage may be:

- Pre-pubertal (rare). In this case puberty will be induced through exogenous hormonal therapy.
- Post-menarche. Even after a few physiologic periods, definite amenorrhea associated with elevated FSH defines a premature menopause.

Loss of estrogens deprives the woman of the lymph that nourishes the female body. Recent data on the widespread tissue distribution of alpha and beta estrogens receptors explain why oestrogen loss affects all

organs and functions [1], differences being accounted for by the complexity of genetic differences, receptor plasticity, interplay among the various hormones and receptors themselves.

Bilateral ovariectomy reduces testosterone production by on average 50%, leading to the so-called "Androgen Insufficiency Syndrome" [2, 3] characterised by loss of libido, loss of vital energy, loss of assertiveness, loss of pubic hair, changes in body shape, possibly contributing to the "fatigue" so often complained of by cancer survivors [4, 5]. Symptoms may be rooted both in biological and psychodynamic factors. Chemotherapy and radiotherapy may not only destroy ovarian follicles, thus causing the oestrogen loss, but may affect the Leydig cells, present in the inner part of the ovary and responsible for androgen production.

All these changes may wound physically and symbolically the *sensuality* and *sexiness*, leading to a self-perception of being defective, broken or damaged, amplified if radiotherapy has caused a narrowing and shortening of the vagina, impairing or preventing intercourse and coital pleasure. Sexuality may be acutely affected also after chemotherapy, usually combined with surgery for ovarian cancers, for its general impact on well-being (fatigue, hair loss, weight changes, nausea and diarrhea, lack of sexual arousal and vaginal lubrication). More so, after radiotherapy, when *sexual dysfunction* is reported on average in 50-82% of patients, even worse after combined surgery and radiotherapy [6-8].

Fertility preservation

Motherhood is a critical part of women's sexual identity. Loss of fertility, secondary to surgery, chemo and/or radiotherapy (pelvic or total body), is a major cause of impaired sense of femininity and loss of sexual interest ("why have sex if I cannot get pregnant anymore?). Unfortunately, when treated for cancer, women of reproductive age are still being inadequately counseled with regard to the negative impact of treatment on their fertility and on their options for fertility preservation. Appropriate information on fertility protection *before* oncologic treatment is essential. Health care providers should therefore know about current possibilities and inform women about fertility protection before cancer treatment begins. This would give patients an extremely powerful message of hope ("if they preserve my fertility, this means that I can be cured and have a child after all…") and maintain a fragment of clear blue sky even in the darkest moments. Moreover, pregnancy after cancer treatment does not seem to worsen the prognosis [9].

Embryo Cryopreservation

Currently the most effective approach. The human embryo is very resistant to damage caused by cryopreservation. The post-thaw survival rate of embryos is in the range of 35-90%, while implantation rates are between 8-30%. If multiple embryos are available for cryopreservation, cumulative pregnancy

rates can reach greater than 60% [10]. Delivery rates per embryo transfer using cryopreserved embryos are reported to be in the range of 18-20% [10]. However, this approach requires *in vitro* fertilization and a participating male partner. This option may not be acceptable to prepubertal or adolescent girls [11].

Cryopreservation Of Mature Oocytes

Oocyte banking is more problematic than cryopreservation of sperms or embryos. The first obstacle is the sensitivity of oocytes to chilling. Cooling and exposure to cryoprotecting agents (CPAs) affect the cytoskeleton and may aggravate the already high incidence of aneuploidy in human oocytes [12]. Exposure to CPAs also causes hardening of the zona pellucida, so that all oocyte cryopreservation protocols involve intracytoplasmic sperm injection (ICSI) as a precaution. Fertilization has to be carried out about 3-5 hours after thawing while the oocyte remains fertile. Further disadvantages of this method are that cancer patients may not have more than one opportunity for oocyte harvesting before undergoing potentially sterilizing treatment, since a cycle of controlled stimulation requires several weeks, and there is normally a delay of a few months before treatment cycles. The success of the method is also dependent on the total number of eggs harvested (<10 oocytes is associated with a very low chance of pregnancy). However, with the introduction of ICSI and the publication of reassuring data [13], efforts to cryopreserve oocytes have resumed in recent years, with conventional slow cooling–rapid thawing protocols and later with vitrification. The overall live birth rate per cryopreserved oocyte is about 2%, which is much lower than that with IVF using fresh oocytes [14].

Cryopreservation Of Immature Oocytes After In Vitro Maturation (IVM) (Without Gonadotropin Stimulation).

Oocytes are recovered for IVM from fresh tissue or follicular aspirates before the dominant follicle emerges during the mid-follicular phase of the menstrual cycle (normally 8-10 mm in diameter). Cryopreservation difficulties include the different optimal times of equilibration for the oocyte and its smaller cumulus cells. At present, the reported success of IVM in young women with polycystic ovaries is a pregnancy rate of approximately 25-30% per cycle, with a high miscarriage rate [15].

GnRH analogue treatment (gonadotropin-releasing hormone analogue, GnRHa)

Keeping the ovarian follicular development quiescent by suppression of gonadotropins has been proposed to protect women from damage by cytotoxic therapy. This research has suggested that receipt of GnRH-a throughout treatment may increase a woman's likelihood of remaining premenopausal after chemotherapy, although there has been an intensive debate concerning the existence of FSH (Follicle

stimulating hormone) receptors in primordial follicles and GnRH-a receptors in the human ovary [16, 17].

Cryopreservation of ovarian tissue

Currently appears to be a very promising way of providing the cancer patient with a realistic chance of fertility preservation –a prospect that is also extremely important for psychological reasons [18]. The cryopreservation of ovarian cortical strips has emerged in recent years as an easy, fast, and inexpensive technique and has already yielded the first live births [19, 20]. The idea of cryopreserving ovarian tissue is based on the finding that the ovarian cortex harbors primordial follicles that are more resistant to cryoinjury than mature oocytes, because the oocytes they contain have a relatively inactive metabolism and lack a metaphase spindle, zona pellucida and cortical granules [21]. Advantages include fewer logistical restrictions, no need for hormonal stimulation, a plus when time is short and a far larger number of oocytes preserved , with a greater fertility potential . Ovarian tissue cryopreservation may also be the only acceptable method for any prepubertal or premenarchal female patients receiving chemotherapy or pelvic radiotherapy [22, 23].

Medical therapies of sexual disorders in cancer survivors

Female sexual disorders have been addressed in previous chapters. Table 1 summarizes sexual issues in women cancer survivors to re-set the scenario where medical therapies are indicated, to ease the reader's comprehensive approach.

Medical therapies of FSD include different interventions, that should be integrated with an appropriate rehabilitative and psychosexual approach (Table 2). The adequate diagnosis of different contributors of the current FSD is mandatory. Physicians should assess if the current complaint preceded cancer treatment, is concomitant to it or caused/worsened by the diagnosis/treatment of cancer per se, i.e. assessing if the disorder is lifelong or acquired. He/she should always evaluate if the etiology is prominently biological, psychosexual or mixed, and if the disorder is generalized or limited to a partner and/or a specific situation [24].

A specific contributor of FSD after cancer treatment is the premature iatrogenic menopause, either due to premature ovarian failure (POF), secondary to chemo and/or radiotherapy, or to surgical removal of both ovaries (surgical menopause). Symptoms and signs may include infertility, mood disorders (depression, loss of self-esteem, relational difficulties), disorders secondary to the estrogenic loss (hot flashes, insomnia, memory difficulties, vaginal dryness, joint pain, osteopenia/osteoporosis) and disorders secondary to the androgenic loss (loss of sexual interest up to Hypoactive Sexual Desire Disorder (HSDD), orgasmic difficulties, fatigue, loss of assertiveness). Different factors may interact contributing to loss of desire (both

in the biologic and motivational component), arousal difficulties (mental and genital), orgasmic difficulties and physical and emotional dissatisfaction. Introital and deep dyspareunia may be comorbid with vaginal dryness and with specific anatomical impairments, specifically after surgery/radiotherapy for cervical cancer.

The most relevant medical therapies will be briefly addressed, with a short paragraph on new potential treatments.

Hormone therapy

Hormonal therapy (HT) is necessary to prevent short and long term systemic and sexual consequences of estrogen and androgen loss [1, 25-27] particularly in young cancer survivors affected by iatrogenic menopause. Estrogens, and progestins if the uterus is conserved, should be prescribed when oncologically appropriate (i.e. with the exception of hormone dependent cancers) in doses adequate for the patient age, to induce regular periods with good cycle control and to maintain optimal stimulation of different tissue oestrogen receptors. The goal is to restore at best the woman's wellbeing, which guarantees the best compliance. Androgens should be considered when women have undergone bilateral ovariectomy, systemic chemotherapy, pelvic or total-body radiotherapy, and/or when symptoms and plasmatic levels are suggestive of *Androgen Insufficiency Syndrome* [28].

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 [1]. This loss accelerates the negative multi-systemic effects of ageing, with a further detrimental effect, which affects sexuality in a complex way. Current key predictors of HT use are: *age at menopause* (the younger the woman, 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); *education and socioeconomic level* (women better educated and with higher socioeconomic background are more likely to use HT). In cancer survivors, those factors are maintained, with the exclusion of hormone-dependent cancers.

HT is 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 positive 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 needs to be further documented in prospective studies.

Hormone therapy encompasses treatment with estrogens, estrogens and progestins, combined estrogen and testosterone, testosterone alone, tibolone and dehydroepiandrosterone sulfate (DHEA-S). Sex

hormones increase the sensitivity of an individual towards sexual stimuli [26, 28]. Estrogens, androgens and progestins modify the 'motivational' state towards or against sexual activity. The distinct effects of estrogens and androgens on desire are still not completely understood and the interplay between these hormones appears to be important. The role of testosterone is relatively well understood; it seems to play a crucial role in sexual desire, arousal and receptivity towards sexual stimuli.

Progesterone has a mild sedative effect on sexuality. Progestins' action on sexuality varies and depends on a number of factors, mainly related to their androgenicity, which is the result of: a) being 19-nor-testosterone derivatives, such as noretisterone; b) having agonistic affinity with the androgenic receptors; c) having competive binding affinity (vs testosterone) to Sex Hormone Binding Globulin (SHBG); d) inhibiting the 5-alpha-reductase type 1, which activates testosterone degradation to dihydrotestosterone. However, to this authors' knowledge, no specific study on progestins alone has been carried out in cancer survivors with a specific focus on sexual symptoms. A few more notes will be specified for each class of hormones to help health care providers to have a clear scenario of key advantages hormones can offer to cancer survivors, when oncologically appropriate. A gynecologist skilled in medical treatments of the menopause and on comorbid sexual disorders can then tailor treatment(s) to the woman's individual needs with the best outcome in terms of personal and couple' sexual satisfaction, while minimizing the cancer-treatment related side effects.

Estrogens

Estrogens used in HT include different hormones (estradiol, estriol, and conjugated estrogens). They are important for the maintenance and function of neurotrophism and neuroplasticity, on one side, of the vaginal epithelium, vascular cells, smooth muscles and nerve trophism on the other. Genital sexual symptoms are more frequent in women with estradiol levels <50 pg/ml [29]. Estrogens have vasodilatory effects and increase vaginal, clitoral and urethral blood flow via nitric oxide synthase (NOS) and vasoactive intestinal polypeptide (VIP) pathways, leading to genital congestion and vaginal lubrication when sexual stimuli occur. Estrogens also modulate sensory thresholds to erotic stimuli.

Several randomized controlled trials have shown a positive effect of systemic estrogen on sexual function in naturally menopausal women [30-34]. Sherwin and co-workers pioneered the research in this field showing that systemic estrogens significantly increase sexual desire and arousal [30, 31]. Wiklund *et al., and* Nathorst-Boos et al. further support this finding [32-34]. Specifically, satisfaction with frequency of sexual activity, sexual fantasies, degree of enjoyment, vaginal lubrication and pain during intercourse were positively influenced in the group who received estradiol compared to the placebo group. However the frequency of orgasm and sexual arousal were not enhanced by estradiol treatment. [32-34].

In practice: Systemic estrogens alone (either oral or transdermal) are indicated in cancer survivors complaining of menopausal symptoms and comorbid sexual disorders related to the estrogen loss, who have been hysterectomized. Contraindication to systemic estrogens include hormone-dependent cancers such as breast and advanced endometrial cancer.

Estrogen and Progestins

Progestins must be added to estrogens when the uterus is preserved. Progestins can better contribute to maintain a good sexual response when they have an androgenic profile, such as noretisterone, as mentioned above.

Estrogen/Androgen Combination Therapy

Androgens play an important role in sexual desire, arousal, orgasm and satisfaction by interacting with receptors in the hypothalamus, with dopaminergic, serotoninergic and opiatergic pathways, and with genitals receptors. Combining androgens and estrogens appears to enhance female sexual function, evidence of which was obtained from studies in estrogen-replete patients, when testosterone was added. [35]

Sherwin *et al*. showed that women receiving combined estrogen/testosterone therapy experienced greater improvement in sexual desire compared to those receiving estrogen alone [31, 36] Sarrel *et al.* showed that estrogen alone is not sufficient for addressing all aspects of sexual function [36]. Adding methyltestosterone to estrogen resulted in significant improvements in sensation, desire and frequency of sexual activity. Somboonporn and co-workers further reviewed the available literature on this subject and assessed 23 trials involving 1957 patients. A pooled estimate from the studies suggests that the addition of testosterone to hormone treatment (HT) regimens improves sexual function scores for postmenopausal women. The authors of this review concluded that there are benefits of combining androgens with estrogen in terms of sexual function. However, studies reviewed in the meta-analysis used different testosterone regimens, making it difficult to estimate the effect of testosterone on sexual function in association with any individual HT regimen [37].

Numerous studies have also investigated the effect of testosterone treatment on psychological variables in estrogen-replete surgically or naturally post-menopausal women. Some of these studies have assessed the effectiveness of testosterone treatment by using parameters such as mood, well-being, vitality and positive well-being Improvements in these parameters have been reported in several studies following the use of testosterone. [38, 39]

In practice: the estroandrogen combination is of special appeal in cancer survivors with comorbidity between sexual and somatopsychic symptoms, after total hysterectomy and bilateral oophorectomy. Androgen may reduce sexual symptoms specifically related to the ovarian androgen loss.

Transdermal Testosterone Specifically for Women

It is worth stressing that testosterone has a powerful trophic impact on the whole woman's body. Meanwhile, it has a powerful neuroplastic and anti-aging effect on the woman' brain. Clinical data indicate that the rebirth of sexual desire is associated with a better global physical and emotional response: physical and psychological excitement, and the ability to reach orgasm, are significantly improved. Furthermore, anxiety and concern are reduced, while the sense of femininity is improved [38].

In practice*:* Testosterone replacement may promote a "co-treatment" of different conditions (co-morbidity): besides sexual desire and related sexual disorders, it may have a very positive impact on mood disorders, fatigue, cognitive impairment, osteopenia, age-related muscle loss, caused or worsened by the lack of testosterone, giving cancer survivors a boost of well-being, even more appreciated as a life-gift after years of sorrow, pain, fatigue and loss of vital energy.

When oncologically appropriate, testosterone, either alone or in combination with estrogen, should be considered after surgical menopause and in those women who complain of AIS and/or specific sexual symptoms (excluding dyspareunia) after chemo or radiotherapy, as the Leydig cells of the ovaries could have been destroyed, even if the gonads are still on site. Further studies are needed to support this claim.

Synthetic Steroids

Tibolone is a synthetic steroid with estrogenic, androgenic and progestogenic properties. It is indicated for the relief of climacteric symptoms in postmenopausal women. Studies have shown that tibolone treatment (1 capsule per day) yields significant improvements in sexual fantasies, arousability, desire for sex with a steady partner and vaginal arousal after erotic stimulation [40].

A further study comparing tibolone and continuous estradiol/norethisterone acetate (E2/NETA) showed that the former resulted in better improvement in frequency of sexual activity, sexual enjoyment and satisfaction compared with the latter [41].

Treatment with tibolone has demonstrated good overall tolerability with a low incidence of vaginal bleeding and breast tenderness. Sexuality, defined by frequency of sexual interest, frequency of orgasm, frequency of sexual responsiveness and frequency of general sexual satisfaction overall significantly improved with HT [41]. However, tibolone and HT with androgenic progestins increased scores to a greater

extent than estrogen replacement therapy. Of note, at the time of writing this, tibolone is marketed in more than 70 countries worldwide, however, not in the USA.

In practice: The main indication of Tibolone is the cancer survivor with non–hormone-dependent cancer, complaining of postmenopausal and sexual symptoms, either after a iatrogenic or spontaneous menopause.

Topical hormonal therapies

Topical estrogen therapy (estradiol, estriol conjugated estrogens, promestriene): may variably contribute to improve genital arousal disorders contributing to vaginal dryness, post-coital cystitis (complained of 24-72 hours after intercourse), comorbid with vaginal dryness and/or introital dyspareunia.

Topical Testosterone therapy: Anecdotically, testosterone propionate powder 2% in vaseline jelly, when applied in minimal quantity to the clitoris and labia once a day, may improve a woman's genital sexual response in 8-10 weeks, with a plateau of response in 16-24 weeks. Specific effects include increased vulvar congestion, more rapid genital arousability, more intense clitoral orgasm, increased number of orgasms, and a sense of "getting back" to a more satisfying and rewarding physical response.

In practice: When oncologically appropriate, topical hormonal treatments may be considered to improve the quality of genital sexual response in women cancer survivors. However, controlled studies in cancer survivors are lacking.

In summary, skilled gynecologists and GPs may tailor HT, when oncologically appropriate, according to the woman needs, with a careful choice of the more appropriate estrogen type (estradiol, estriol, conjugated estrogens) and dose; type and dose of progesterone or progestins; testosterone, when indicated to maximize the benefit on the general wellbeing and specifically on sexuality of cancer survivors. Tibolone may be a valid alternative. Careful choice of the route of administration, with preference for transdermal and/or vaginal treatment to reduce liver first pass, may further enhance compliance, adherence and consistency of use with increasing satisfaction on both general and sexual well-being, while contributing to minimize long term side effects of cancer-related treatments.

Non-hormonal Central nervous system acting drugs

The role of the CNS in women's sexuality is strong but has remained under-researched. 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

(e.g., gonadotropin-releasing hormone, luteinizing hormone, testosterone, prolactin and endorphins) involved in sexual functional capacity.

Antidepressants In Sexual Problems And Depression

Cancer survivors face mood changes, including potentially, clinically relevant depression in the many cases (Table 3). Contributors include physical, emotional and relational factors. Depression is comorbid with loss of desire in more than 50% of cases. Unfortunately, the majority of antidepressants, with the exception of bupropion, have an anti-sexual effect in a dose dependent pattern [42, 43].

Bupropion

This is an antidepressant with a peculiar effect of sexual function. There is some evidence that bupropion does not share the inhibiting effect other SSRI have on sexual function [44]. Bupropion may have different impact on dopamine transport than other antidepressants [45]. 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 [44, 45]. 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.

Depression has a different severity and responsiveness to treatment according to the estrogenic state. Specifically, postmenopausal depression is more severe, has a more insidious course, is more resistant to conventional antidepressants in comparison with the premenopausal women and has better outcomes when antidepressants are combined with hormonal therapy [38, 46]

It has been suggested that a chronic hypoestrogenic state, that impairs neuroplasticity, may contemporaneously reduce the response to antidepressant drugs. Controlled studies indicate that post-menopausal women with major depressive disorder based on DSM-IV criteria, who were not on HRT, showed a significantly poorer response to antidepressants over 6 weeks of treatment, compared to the response of pre-menopausal women. Menopausal status and older age are predictors of a poorer response to antidepressant treatment [46].This suggests as well a poorer response to pharmacologic treatments aimed at reducing HSDD associated with depression in postmenopausal cancer survivors

Synergy between antidepressants and HRT in addressing sexual disorders

An increasing body of evidence suggests that a hypoestrogenic postmenopausal status increases the

vulnerability to depression and decreases the effect of antidepressant drugs [46-48].

Animal studies support the synergistic role of estrogen and SSRI in optimizing the antidepressant response, evaluated through specific behavioral tests [49]. In line with this, Thase et al investigated whether differences in antidepressant efficacy are moderated by an interaction of age and gender. A pooled dataset from eight randomized, controlled trials of patients with major depressive disorder (MDD) was reanalyzed. Among women there was a significant interaction reflecting poorer SSRI response in the older age group; HT appeared to eliminate this difference. These findings provide further evidence that age, gender, and HT moderate response to antidepressant medications [50].

Estrogen therapy (ET) may also play a role in antidepressant response in postmenopausal women with major depressive disorder by accelerating the antidepressant response [51] or even potentiating antidepressant medication effect thus improving mood. ET demonstrates a specific efficacy in those depressive disorders during iatrogenic menopause consequent to chemotherapy [52].

In practice: the synergy between antidepressants and hormone therapy in women with either natural or iatrogenic menopause and depression is of the highest importance to improve their quality of life. (QOL) However, to the author's knowledge, no specific studies focused on response to treatment in postmenopausal cancer patients with comorbidity between depression and sexual symptoms have been conducted. Meanwhile, the author's clinical experience indicates that low dose of antidepressant combined with well-tailored HT may maximize the QOL and sexuality of cancer survivors, while minimizing side-effects ad risks .

Antidepressant Drugs In The Treatment Of Menopausal And Sexual Symptoms .

Antidepressants can reduce some menopausal symptoms (specifically hot flushes and insomnia) when they act on common neuro-biological denominators. Soares and Coll found a similar efficacy between HT and escitalopram in curing depressive symptoms and menopausal symptoms as vasomotor symptoms and insomnia [53]. After hormone therapy discontinuation, paroxetine offers a better control of menopausal hot flushes over placebo [54, 55]. These observations may result useful for those women who have a contraindication to HT (56-60] such as breast cancer patients, or those who prefer to stop HT and address their neurovegetative and affective symptoms in a non-hormonal way. However, it should be remembered that SSRI address only a few neurovegetative symptoms, beside depression, but cannot modulate the many others symptoms caused by the estrogen loss (such as joint pain, vaginal dryness, worsened urge incontinence, etc.)

Non hormonal topical treatments

Vasoactive agents in women

The development of PDE5 inhibitor (PDE5i) therapy for erectile dysfunction in men in 1998 revolutionized the treatment of male sexual dysfunction [61]. Preclinical work with clitoral tissue baths suggested a rationale for use of these agents in female dysfunction [62]. Research to date regarding use of PDE5i in women has not shown a consistent benefit to this approach [63] Attempts to gain a regulatory indication of any of the available PDE5i for female sexual dysfunction seem to have been abandoned. Anecdotically, there may remain a PDE5i indication in women with maintained sexual desire who complain of vaginal dryness specifically due to vascular genital factors (in synergy with topical estrogen/androgen treatment) after genital radiotherapy.

Botulin toxin

Since the late 1970s botulinum toxin (BoT) has been used as a therapeutic tool. BoT reduces muscular activity by inducing a pre-synaptic 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. [64]. Historically, 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 agents 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 72-85%.

A subset of patients 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 the pelvic floor muscles (levator ani or outer third vagina muscles) improves symptomatology in patients with vaginismus, addressing the specific myogenic hyperactivity of the levator ani [65, 66] . Integrated with a multimodal treatment (pharmacologic with SSRI and benzodiazepines, pelvic floor physiotherapy, and focused psychosexual therapy) contributes to restore the possibility of intercourse leading to a more complete sexual life. BoT 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. [65, 66].

In practice: BoT treatment may have a role in hyperactive pelvic floors of cancer survivors who: a) had a primary vaginismus they decided to treat after having being diagnosed with and treated for cancer; b) have a recurrence of vaginismus after cancer treatment and/or for coexisting biological triggering factors; c) have a hyperactive pelvic floor associated with vulvar vestibulitis/vulvodynia, not responding to standard pharmacologic and rehabilitative treatments. However, specific studies on cancer patients using BoT have not been carried out so far.

Future treatment options

On-going research suggests that new central nervous system (CNS) acting drugs may be of interest in the medical treatment of FSD in cancer survivors

Flibanserin

Flibanserin is a post-synaptic 5-HT_{1A} agonist, a very weak partial agonist of dopamine D(4) and a 5-HT_{2A} antagonist [67]. As current antidepressants exert an acute effect at the pre-synaptic level, almost all block the uptake of monoamines or inhibit the activity 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. These phenomena need time for induction [68]. Recently a new potential therapeutic combination has been proposed in which a serotonin 5-HT_9 uptake blocker is administered together with pindolol, an antagonist of the pre-synaptic 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 comorbidity between depression and HSDD, an antidepressant with a specific action on the prefrontal cortex (besides hippocampus and midbrain) could represent a new option for HSDD.

Flibanserin seems to satisfy the need of a short acting drug and is currently under development for hypoactive sexual desire disorders (HSDD) and female central sexual arousal disorders [67-70]. Flibanserin may be of special interest in cancer survivors of hormone dependent cancers, who complain of FSD and

cannot use conventional HT. However, to the author's knowledge no studies on this important subset of cancer survivors have been carried out at the time of this chapter writing.

***In practice**:* once and if efficacy is proven, 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 sexual therapy. The future of sexual medicine in general and of the treatment of FSD in particular may be aided most 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 [69,70]. 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, specifically in cancer survivors.

Psychosocial Interventions

Psychosocial interventions include basic counseling, physiotherapy and psychosexual intervention. Basic sexual counseling is an integral part of medical consultation. An initial session can involve the practitioner providing the patient with information on anatomy and physiology, sexual development and function, fertility, sexuality in different life phases, the spectrum of human sexual behavior and cultural norms and communication of sexual needs. This information is intended to elicit understanding and encourage questions with the hope of increasing the patient's knowledge of and self-confidence in their sexuality, more so after the difficult and challenging experience of being diagnosed with and treated for cancer.

Psychosocial interventions are excellent tools for addressing FSD and it is normally the case that biomedical and psychosocial interventions are combined to provide an optimal outcome. This type of therapy is best considered as a step-by-step approach with continuous adaptation of diagnosis and therapeutic strategies, more so in cancer survivors.

Conclusion

Cancer is increasingly more of a chronic than a fatal disease. More attention should be focused on restoring a satisfying QOL, which includes physical intimacy, sensuality, and sexuality. Unfortunately, sexual problems are usually neglected in female cancer survivors, with a specific denial of their biological basis, with symptoms being attributed to the negative psychological effect of cancer diagnosis and treatment per se and their negative affective consequences such as depression and anxiety. Opposite to this psychologically-oriented approach, medical and rehabilitative treatments can offer substantial improvements, certainly more so when combined with appropriate psychosexual counseling. Indeed, the contextual sensitivity of female sexual response tends to 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.

In clinical practice, hormonal treatments, currently used to treat menopausal symptoms, should be considered more often to improve sexuality as a critical part of a rewarding quality of life and aging in non-hormone dependent cancer survivors . When oncologically appropriate, different hormone combinations, inclusive of estro-androgen or testosterone alone, may be tailored according to the individual needs. Combinations of antidepressant and HT may further aid women with depression and sexual symptoms after a natural or iatrogenic menopause for cancer.

New non-hormonal agents, such as flibanserin are currently investigated and could offer an option for younger cancer survivors with HSDD who cannot or would not take hormones to improve their desire and sexuality. However, data in cancer patients have not been produced so far.

While the recent data supporting the therapeutic use of centrally acting agents, as a monotherapy for FSD, is cautiously encouraging, there is a tremendous promise for these centrally acting compounds to be integrated into treatment approaches that utilize other pathways in a multi-layered, individualized 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, whatever the disease the patient is complaining of. The goal is to give women and couples the full potential of a joyful sexuality in their lifespan, in spite of and over the challenge of the cancer experience.

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Table 1: Factors contributing to sexual dysfunction after cancer in women

Sexual desire may be affected by:

- *sexual identity related issues*: body image impairment, disfiguring cosmetic outcomes, negative sexual self schema, premature ovarian failure, sterility, missed accomplishment of life cycle goals;
- *loss of sexual hormones* and Androgen Insufficiency Syndrome;
- *cancer treatment's long lasting side effects*: severe fatigue, cognitive impairment, conditioned nausea, mouth sores, cough, hair loss, headache, especially in post Bone Marrow Transplant (BMT) patients; worse QoL; post-traumatic stress disorder (considering cancer a major traumatic experience);
- *secondarily,* because of concomitant sexual arousal disorders, orgasmic difficulties and/or sexual pain disorders; negative relational factors (distant/indifferent or abusive partner; partners' emotional and/or sexual problem, cancer related or independent)

Sexual arousal may be affected by:

- *inadequate central arousal* ,, due to the *d*eprivation of sexual hormones –specifically androgens- mostly in women suffering from AIS, and the overlapping effect of factors inhibiting sexual drive;
- *genital arousal impairment,* due to loss of sexual hormones and iatrogenic anatomic, vascular and nervous damage, particularly after genital cancers
- *non-genital-peripheral arousal, because of the reduced sexua*l repertoire and loss of sexual hormones
- couple problems, more significant in younger couples, affecting motivation, self confidence, intimacy and attachment dynamics

Sexual pain related disorders, may be determined by:

- vaginal dryness, secondary to arousal disorders of mixed origin; vaginal anatomical shortening and functional impairment, in consequence of pelvic surgery and/or radiotherapy
- defensive contraction of the pelvic floor muscles, leading to myalgia with tender and trigger points, contributing to introital pain at penetration

Orgasm and pleasure may be affected by the impairment of:

- sex drive and arousal disorders, of mixed biological and psychosexual origin; specific effect of AIS on clitoral responsiveness
- reduced "orgasmic platform" for the loss of estrogens and vaginal anatomical damages (more frequent in cervical cancer survivors)

Sexual satisfaction may be physically and emotionally affected:

- *physical* satisfaction is more vulnerable in younger women, when low desire, inadequate central and genital arousal, orgasmic difficulties and/or dyspareunia are complained of.
- *emotional satisfaction* may be maintained, when closeness and quality of intimacy is strengthened by the cancer experience. It can be worsened when cancer triggers a further physical and emotional distance and loss of communication and support between partners .

The highest vulnerability is described in younger, single, and of low socio-economic status, or women living in a couple with conflicts

Table 2: Integrative Approach When Addressing Sexual Disorders In Women Cancer Survivors

Medical :

- appropriate and timely HT, local and systemic, except for hormone-dependent cancers, in all young cancer survivors affected by iatrogenic menopause
- in patients treated for gynecologic and/or other pelvic cancers: treatment of inflammatory and/or atrophic conditions
- specific treatments of medical basis of FSD (antidepressant, analgesics…)

Rehabilitative :

- moulds or dilators & lubricants to improve vaginal shortening and reduced elasticity;
- local vaginal stretching and self-massage with medicated oil, to improve elasticity and restore positive attention to this part of the body
- physiotherapic rehabilitation of the pelvic floor, after pelvic surgery/radiotherapy

Psychosexual:

- individual and couple psychosex**ual support** open to body image, intimacy, and attachment issues, and to relational contributors of FSD
- good doctor-patient relationshi**p, open to l**istening to sexual concerns (up to 80% of physician never raise the sexual issues in oncologic consultations)

Table 3: Depression and anxiety as cofactors for FSD in cancer survivors [38]

Depression and anxiety as cofactors of FSD in cancer survivors

Depression and anxiety reactive to cancer per se and secondary complications (e.g after radiation-induced diarrhea or voiding disorders, when they persist after radiotherapy,) may further affect erotic perception, self -esteem and sexual self-schema. Women are more vulnerable than men to depression, from puberty onwards. Hormonal changes during menopausal transition may contribute to a specific “window of vulnerability.”, more severe in women with iatrogenic premature menopause

Gender differences, related to varying sexual hormone levels and hormone secretion patterns across the lifespan, contribute to women's vulnerability to mood disorders and major depression. Depression across the menopause has a multifactorial aetiology, which is complicated by cancer related factors in cancer survivors .

Predictive factors include: previous depressive episodes such as premenstrual syndrome and/or postpartum depression; co-morbidity with major menopausal symptoms, especially hot flashes, nocturnal sweating, insomnia; menopause not treated with HT; major existential stress; elevated body mass index; low socioeconomic level and ethnicity. Postmenopausal depression is more severe, has a more insidious course, is more resistant to conventional antidepressants in comparison with premenopausal women.