Sexual Dysfunction 1

Sexual sequelae of general medical disorders

Rosemary Basson, Willibrord Weijmar Schultz

Summary

That sexual symptoms can signal serious underlying disease confirms the importance of sexual enquiry as an integral component of medical assessment. Data on sexual function are sparse in some medical specialties. However, increased scientific understanding of the central and peripheral physiology of sexual response could help to identify the pathophysiology of sexual dysfunction from disease and medical interventions, and also to ameliorate or prevent some dysfunctions. Many common general medical disorders have negative effects on desire, arousal, orgasm, ejaculation, and freedom from pain during sex. Chronic disease also interferes indirectly with sexual function, by altering relationships and self-image and causing fatigue, pain, disfigurement, and dependency. Current approaches to assessment of sexual dysfunction are based on models that combine psychological and biological aspects.

Introduction

Medical understanding of sexual responses has increased substantially in the past 15 years. Neurotransmitters and endothelial factors that mediate genital congestion have been identified—albeit with far more data in men than in women. More recently, brain imaging techniques have afforded a window on the neurological circuits that appraise and process sexual stimuli: the intricacies of the “gyrus fornicatus” (cingulate gyrus) discovered by anatomists a century ago are now being unravelled.

This sexual medicine series reviews the accumulating data on the comorbidity of sexual and other medical disorders. Diseases and medical interventions can directly interfere with central and peripheral sexual physiology. However, the traditional dualistic notion that sexual dysfunction has either psychological or organic origins has been replaced by an understanding that the two are inseparably combined. Psychological factors such as personality, coping style, and external stressors can modulate immune, inflammatory, endocrine, and neurological mechanisms. Furthermore, medical disease has psychological repercussions that could potentially disrupt physiology. Although in its early stages, functional brain imaging is beginning to clarify the modulation of sexual response by psychological and medical factors. Such factors can predispose to, precipitate, or maintain sexual dysfunction, and therefore they need to be considered.

We outline the general medical disorders and treatments that interfere with sexual motivation, desire, subjective arousal and excitement, orgasm, pleasure, and freedom from pain. We also discuss the physical response of genital congestion that is organised by the autonomic-nervous system. Two very common dysfunctions—vascular erectile dysfunction and dyspareunia from vulvar vestibulitis syndrome—are addressed in detail. The other two articles in this series review the sexual sequelae of specific neurological and endocrine disorders.

Data about the concurrence of sexual dysfunction with many medical disorders are scarce. Well-validated questionnaires about sexual dysfunction, tested in a range of languages, have only recently become available. Some questionnaires focus on genital issues rather than subjective responses even though, in both men and women, the two do not always correlate. Despite evidence to the contrary, the assumption that women regularly sense desire in between sexual experiences, as men do, is common. Some investigators advocate that validated diagnostic methods should be revised to more accurately correspond to contemporary ideas about the sexual responses of men and women, and to up-to-date definitions of women’s dysfunction (although these have yet been incorporated into official definitions of mental disorders). Many studies include only patients in stable relationships or those who are sexually active, and thus exclude those for whom sexual dysfunction has precluded sexual activities or relationships.

The available studies of the prevalence of dysfunctions are derived from clinical samples of widely varying size, with and without controls; the levels of evidence for treatment diverge widely. Throughout the series, we cite case-control prevalence studies and randomised controlled treatment trials, but where unavailable we refer...
to treatment based on open-label studies or clinical experience (personal and from published work) and note the limitations of the evidence.

### Sexual function and dysfunction

Sexual dysfunction can herald serious underlying disease. Onset of erectile dysfunction, the most common sexual disorder in older men, is seen as a pointer to generalised endothelial dysfunction, which invites assessment of cardiovascular health and, in particular, the health of coronary arteries. One study showed that, of 132 men who received coronary angiographies, 45% had a history of erectile dysfunction, which preceded the diagnosis of coronary artery disease in 58% of these men.46 In a retrospective cohort study of 26 000 men in good general health, with a mean age of 40 years, who were registered in an integrated health-information bank, and followed up for an average of 1 year, a two-fold increase in the risk of myocardial infarction was identified in the 13 000 men with erectile dysfunction at baseline.47 Endothelial dysfunction in the brachial arteries of men who are presumed to have vascular erectile dysfunction, but have no other evidence of cardiovascular disease, could identify those who are particularly at risk.48 A study screening for erectile dysfunction in a health centre showed undiagnosed diabetes, hypertension, and other comorbid disorders in a third of 125 affected men.39 Low sexual desire in combination with an abnormally low concentration of

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<td>Coronary artery disease, myocardial</td>
<td>Low motivation to trigger</td>
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<td>infarction, or both: most patients</td>
<td>desire or act upon it because</td>
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<td>reduce frequency of sexual activity</td>
<td>of fear of further MI.</td>
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<td>Renal failure: low desire in 45–100%</td>
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<td>symptoms including urinary incontin-</td>
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<td>ence. Odds ratio of 2 for stress</td>
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<td>incontinence.</td>
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<td>Diabetes: prevalence of low desire</td>
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<td>in men and women with diabetes</td>
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<td>uncertain.</td>
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<td>painful from oestrogen</td>
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<td>deficiency and associated</td>
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<td>dyspareunia.</td>
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<td>Hyperprolactinaemia.</td>
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<td>Perform definitive therapy</td>
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<td>for incontinence—but surgical</td>
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<td>intervention caused worsening</td>
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<td>sexual function in 71% and</td>
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<td>improved sexual function in</td>
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<td>only 29%.47 Postmenopausal</td>
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<td>oestrogen therapy does not</td>
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<td>associated with infection.67</td>
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<td>Improve glycaemic control.</td>
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<td>Address underlying cause by</td>
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<td>medical or surgical management.</td>
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<td>In men: primary or secondary</td>
<td>Lack of testosterone affects</td>
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<td>hypogonadism</td>
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<td>stimuli.1</td>
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<td>In women: bilateral oophorectomy.</td>
<td>Loss of ovarian testosterone</td>
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<td>and androstenedione (precursor</td>
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<td>of oestrogen and testosterone).</td>
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<td></td>
<td>Supplementation of oestrogen</td>
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<td>alone might not restore desire.</td>
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testosterone in the blood (hypotestosteronaemia) can signal imminently treatable disorders such as haemochromatosis or pituitary adenoma. Furthermore in women, disorders of mental health, especially depression, underlie the presentation of low desire in some 17–26% of cases. In the context of renal failure, diabetes, or multiple sclerosis, comorbid depression elevates the prevalence of sexual dysfunction beyond that of the general population. If the sexual effects of medical treatment are ignored, they could diminish patients' compliance with medication, and thus result in low desire. The presentation of low desire in some men and women is common—especially in women. Low desire can accompany other sexual dysfunctions, which are more likely with pontine lesions.

Head injury. Direct damage to regions involved in processing sexual stimuli.

Hypothalamic or pituitary damage, or both. Only one of six small RCTs of DHEA showed sexual benefit in women.

**Disorders of sexual desire and sexual motivation**

**Hypoactive sexual desire**

Men and women have multiple incentives and reasons for initiation of, or agreement to have, partnered sexual activity. One reason is to fulfil desire, or so-called sexual drive, which is typically sensed daily or more often by young and middle-aged men and by women who are in the early phases of sexual relationships, but infrequently in most middle-aged women, despite the fact that they report satisfactory sexual lives. Thus, the definition of hypoactive sexual desire disorder in women is a subject of continuing debate. Past definitions have been more appropriate to male sexuality, with a focus on sexual thoughts, sexual fantasies, and desire for sex before the sexual encounter.

Various diseases interfere with sexual desire (table 1). As do some treatments; these range from the obvious (eg, bilateral oophorectomy or orchietomy) to the less obvious (eg, suppression of the hypothalamic pituitary axis by corticosteroids, which reduces production of adrenal prohormones such as androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate). A connection between low desire and depression is ubiquitous and might be compounded by selective serotonin reuptake inhibitors. Other factors can affect individual susceptibility to hypoactive sexual desire; for example, independent assessments show that patients with both a history of psychological or physical abuse and a gynaecological disorder (but not a gynaecological disorder alone) had lower sexual desire.

**Reduced sexual motivation**

Other than sexual desire, the reasons for engaging in partnered sex can include generation of emotional closeness, confirmation that an argument has been resolved, or reassurance of a loving relationship despite...
illness or disfigurement. In both men and women, motivation is influenced by many circumstantial factors\(^1\),\(^2\),\(^2\),\(^2\),\(^2\),\(^2\) such as interpersonal difficulties, low self-image, absence of needed sexual stimuli or sexual skills in either partner, or issues about privacy or safety. A difficult sexual response—ie, no arousal, no erection, or disinclination to engage in sexual behaviour—can be seen as simply adaptive, rather than dysfunctional.\(^6\) Factors that commonly interfere with sexual motivation and response should be assessed in the context of additional contributions from chronic illness.

### Disorders of sexual response

Accepted models of human sexual response are circular, and consist of overlapping phases, in a variable order,\(^3\),\(^2\) with some responses more characteristic of one sex than the other. Men (commonly) and women (sometimes) have a sense of desire at the beginning of a sexual experience. Although this desire might be absent initially, a person can become motivated to sexually engage.\(^2\),\(^2\),\(^2\) Figure 1\(^a\) shows that desire can be triggered later during the experience once the person is subjectively aroused, with the result that arousal and desire become indistinguishable.

Despite frequent absence of desire at the outset of sexual engagement, women can report satisfactory sexual outcomes.\(^1\),\(^2\) As a result, the definitions of sexual disorder and dysfunction for women have been revised.\(^1\) Lack of sexual desire at the beginning of a sexual experience is no longer always thought to indicate a hypoactive sexual-desire disorder. Rather, it is the recurrent and consistent incapacity to trigger any desire or arousal that constitutes disorder. Despite acknowledgment that men can also be sexually neutral at the beginning of an encounter, and become aroused into sexual desire,\(^9\) recommendations to revise the definition of male sexual-desire disorder have not yet been published. Diagnostic categories, for both men and women, refer to the different phases of sexual response, but now acknowledge that dysfunction in women typically affects all phases\(^9\),\(^9\) and in men less commonly so.\(^9\),\(^9\)

Traditionally, sexual disorders were diagnosed in the case of either personal or interpersonal distress in addition to the abnormal response. The latest revisions to definitions of women’s disorders add a descriptor for the degree of personal distress (whether none, mild, moderate, or severe) to a statement of the diagnosis.\(^9\)

### Functional and dysfunctional arousal: genital studies

Sexual arousal consists of the mind’s processing of internal sexual stimuli (eg, fantasy) and external sexual stimuli, and their context. Psychological responses (cognitive, emotional, and motivational) are appraised, as are the reflexive changes within the autonomic nervous system. Healthy men can accurately assess their own genital engorgement, which correlates with subjective arousal and encourages further arousal (excitement). By contrast, the correlation between the subjective arousal of healthy women and measures of increased vaginal congestion is highly variable—as recorded by vaginal photoplethysmography\(^9\) or by ultrasound measures of clitoral blood flow.\(^9\) Similarly, the correlation between increases in clitoral volume, as measured by MRI, and women’s subjective arousal as they view erotica is minimal, according to preliminary studies.\(^3\)

Healthy men with situational erectile dysfunction (ie, normal nocturnal and morning erections, but difficult sexual erections) usually underrate their erectile response to stimuli.\(^9\) Women with chronic complaints of low arousal typically do not sense subjective arousal or genital congestion when watching erotic videos, and yet, simultaneous assessment of vaginal engorgement shows increases in vaginal congestion that are similar to those in control women.\(^9\) Research also suggests that triggers for women’s genital arousal might be less specific than men’s. Women, but not men, who watched visual stimuli

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**Figure 1:** Circular model of human sexual response, showing cycle of overlapping phases. The sexual and nonsexual outcome influences future sexual motivation

Adapted from Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 2001;\(^4\) with permission from Lippincott Williams & Wilkins.

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**Figure 2:** Model of sexual arousal

ANS=autonomic nervous system. Brain areas activated during arousal to allow sexual feelings, to maintain focus on the sexual stimuli, to anticipate reward, to form a mental image of sexual behaviour, to limit actual behaviour despite arousal, and to elicit autonomic nervous system responses of physical sexual arousal.\(^3\),\(^4\),\(^6\),\(^6\)
that was considered by these healthy volunteers to be sexual but not erotic or arousing (eg, videos of primates mating), had evidence of genital congestion as measured with vaginal and penile photoplethysmography.25

Functional and dysfunctional arousal: brain imaging studies

Functional brain imaging studies to delineate the neural circuits implicated in sexual arousal also attempt to explore differences between men and women and between people with and without sexual dysfunction. The use of PET for brain imaging of healthy people during visual sexual stimulation identifies a model of sexual arousal that includes complex brain circuitry, such as the cortical, limbic, and paralimbic regions that are known to be associated with cognition, motivation, and emotions, linking to changes within the autonomic nervous system.13,55 Figures 2 and 3 integrate these findings with the current model of triggered and initial desire and also with psychophysiological studies of subjective arousal and genital congestion.

In sexually healthy men, brain imaging in response to visual erotica shows robust correlation between subjective sexual arousal and activation in regions of the brain that organise the genital response.73 This correlation has not been reported in sexually healthy women.73 Moreover, we do not yet know which neural systems mediate arousal in women. In a recent study of 28 healthy men and women who watched erotic stimuli, subjective reports of arousal were similar, and many regions of the brain were activated in both men and women.73 However, in women this activation was no greater for sexually explicit stimuli than for scenes of warm but non-sexual interaction between couples.73 These neutral scenes still caused activation in the hypothalamus in men—perhaps in keeping with men’s tendency to interpret many stimuli as subtly (or at least potentially) sexual.74

Overview of pathophysiology of deficient genital congestion

Deficient genital congestion presents as erectile dysfunction in men. In women, a similar deficiency can present as dyspareunia, due to insufficient vaginal lubrication, or as genital arousal disorder. This disorder is defined as absence of vulval swelling or vaginal lubrication from any type of sexual stimulation, with reduced sexual sensations from caressing genitalia, yet with preservation of subjective sexual excitement from non-genital sexual stimuli.74

Genital congestion in response to sexual stimulation results from relaxation of vascular smooth muscle, with the result that arteries dilate, to fill the enlarging sinusoidal spaces within cavernous tissue of either the penis or the clitoral and bulbar tissue. Much more research has been done to investigate penile physiology than vulval physiology. The main neurotransmitter that mediates penile and clitoral smooth muscle relaxation is nitric oxide (NO), which is derived from autonomic nerves. Acetylcholine is released as a co-transmitter. Another source of NO is the endothelium—its release is evoked from postganglionic cholinergic nerves, shear stress, and substances such as oxygen in plasma. Nerve-derived NO is thought to initiate most smooth muscle relaxation, whereas endothelial NO contributes to maintenance of the relaxed state.75 Penile-resistance arteries relax by an additional endothelium-independent mechanism, which is attributed to a hyperpolarising factor, mediated by Ca++ activated K+ channels. NO acts on guanylyl cyclase to generate cyclic guanosine monophosphate (cGMP), and the subsequent cascade of dilator signals provide the basis for phosphodiesterase type 5 (PDE5) inhibition of cGMP by sildenafil, vardenafil, and tadalafl to ameliorate erectile dysfunction.76 Benefit from these medications is dependent on adequate sexual stimulation and on the retention of some capacity to generate endothelial and neurogenic NO. Once tissue expansion is sufficient, the veins that exit the trabecular tissue through the tough fibrous capsule are compressed, which prevents further escape of blood (veno-occlusion). Thus, in the penis, the high flow of the developing erection is converted to the low flow of a fully erect penis.

Veno-occlusion does not seem to be a key factor in female clitoral and bulbar response.28 Neurotransmission of vaginal muscle and vaginal vascular smooth-muscle is less clear; vasoactive intestinal peptide acts via cyclic adenosine monophosphate (cAMP) and is itself degraded by neutral endopeptidase. Increased blood flow through the vaginal submucosal plexus increases the formation of interstitial fluid, which percolates between vaginal epithelial cells into the lumen as sexual lubrication.

In both men and women, genital detumescence and decreased engorgement are mediated by adrenergic constriction of the inflow arteries, which decreases tissue
pressure and facilitates egress of blood through the veins. Other factors associated with smooth-muscle constriction that maintains flaccidity and detumescence might include endothelin-1 and constrictor prostanooids, such as thromboxane A2 and angiotensin II. These excitatory substances cause intracellular free calcium to increase, which transiently activates calcium-calmodulin-dependent myosin light chain kinase, and initiates smooth-muscle contraction. Calcium sensitisation pathways then take over. One such pathway is associated with RhoA, a small G-protein that activates rho-kinase, which in turn inhibits myosin phosphatase, and thereby maintains contractile tone. The consensus is that the phasic contraction of penile smooth muscle is regulated by an increase in calcium and the tonic contraction is governed by calcium sensitisation pathways.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology of sexual dysfunction</th>
<th>Therapy and general comments</th>
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<tr>
<td>Coronary artery disease: prevalence of ED 44%–65%</td>
<td>Endothelial dysfunction, structural atheromatous change, loss of smooth muscle from ischaemia, or cavernosal fibrosis—all leading to impaired venous occlusion.</td>
<td>Give PDE5is, assuming no nitrate therapy. Use caution with α-blockers, hypotension, aortic stenosis, LV outflow obstruction, and unstable angina. Avoid vardenafil with patients with congenital long QT and IA anti-arrhythmic drugs. Recommend weight loss and exercise. D1/D2 receptor agonist apomorphine stimulates erections centrally, and is available in Europe. Not contraindicated in presence of nitrates. Some benefit for mild ED.</td>
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<tr>
<td>Renal failure: prevalence 55%–85% in men with uraemia or on peritoneal dialysis, haemodialysis, or both, with further increase after transplantation</td>
<td>Endothelial dysfunction from associated HT and DM. Reduced NO production associated with increased production of dimethyl arginine. Structural changes in cavernosal smooth muscle. Uraemia-associated reduced bioavailability of L-arginine, reduced NOS expression, quenching of NO by increased reactive-oxygen species and inhibition of NOS. ANS dysfunction associated with uraemia. Penile artery occlusion associated with interruption of internal iliac for placement of pelvic kidney.</td>
<td>Antagonists of renin angiotensin system and calcium channel antagonists could potentially improve endothelial function, but have not been investigated in renal failure. Give PDE5is, which may enhance action of remaining NO.</td>
</tr>
<tr>
<td>Lower urinary tract symptoms: odds ratio 2 to 7</td>
<td>Increased smooth muscle tone from heightened sympathetic nervous system activity. Reduced NOS in cavernous nerves and nerves to bladder outlet. Increased smooth muscle Rho-kinase activity. Smooth muscle fibrosis from ischaemia.</td>
<td>Of the uroselective α-blockers, alfuzosin is associated with less exaculatory dysfunction than tamsulosin. Could possibly combine α-blockers with PDE5is (other than vardenafil)—but no evidence from RCTs.</td>
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<tr>
<td>Cardiac failure: prevalence of ED is up to 80%</td>
<td>Associated CAD, HT, or both.</td>
<td>Caution recommended with erectile enhancement because of risk of hypotension. Preliminary evidence of benefit from PDE5is for exercise tolerance and reduction of endothelial dysfunction in patients with heart failure. Level 1 evidence of benefit from sildenafil if SSRIs are necessary and ED persists.</td>
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<tr>
<td>Hypertension: odds ratio 1.3 to 1.77</td>
<td>Endothelial dysfunction.</td>
<td>Calcium-channel blockers and angiotensin renin antagonists might improve endothelial function. PDE5is are effective in 70% of men with hypertension; however, use caution with α-blockers, and note that vardenafil is contraindicated.</td>
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<tr>
<td>Diabetes: odds ratio 1.5 to 3.95</td>
<td>Reduced NOS activity is possibly because of overexpression of arginase. Lack of NADPH, which is an essential co-factor for NOS. Reduced NADPH also promotes smooth muscle contractility by increasing DAG and protein kinase C. Reduced endothelium-derived hyperpolarising factor. Increased oxygen free radicals including those from advanced glycosylation end-products quench released NO.</td>
<td>PDE5is are effective in about 55% of men with DM. Future NO-releasing PDE5is could prove useful when endogenous NO is severely deficient. Intracavernosal PGE1 is usually effective. Titrination to 20-40 μg typically needed because of vascular impairment.</td>
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<tr>
<td>Primary and secondary hypogonadism: low testosterone is responsible for just 4%–5% of ED. Erections are still possible from visual stimuli.</td>
<td>Low testosterone reduces availability of NO. Associated low desire limits focus on sexual stimuli.</td>
<td>Address cause of secondary low testosterone. Supplement if no contraindications.</td>
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<tr>
<td>Depression: ED present in 26%–50% of untreated patients</td>
<td>Neurotransmitters of frontal limbic circuitry thought to be affected in depression.</td>
<td>Effectively treating ED can encourage remission of depression. ED improved with sildenafil in 50% of men vs 20% with continuous positive airway pressure—trials of combined treatment have been advocated.</td>
</tr>
<tr>
<td>Sleep apnoea: severe obstructive sleep apnoea independently associated with ED</td>
<td>Possible dysfunction of ANS and endothelial dysfunction associated with nocturnal hypoxia, nocturnal hypertension, and nocturnal over-activity of sympathetic nervous system.</td>
<td>PDE5is of benefit when some NO is still released from penile autonomic in response to stimulation (ie, ineffective in non-nerve sparing pelvic cancer surgery, can enhance erections from psychological stimuli in men with complete SCI affecting lumbar sacral cord given intact thoracolumbar outflow). Intracavernosal PGE1 usually effective—use smallest dose e.g. 2 μg and titrate in small increments to avoid priapism.</td>
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odds ratios for comorbid disorders are 1·3–1·77 for mechanisms of erectile dysfunction associated with women. The probable pathological and physiological far more in the genital vasculature of men than in that of diabetes, hyperlipidaemia, and smoking have been studied.

[Footnotes: Table 2: Drugs and associated erectile dysfunction

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**Erectile dysfunction**

The effects of atheroma, hypertension, renal failure, diabetes, hyperlipidaemia, and smoking have been studied far more in the genital vasculature of men than in that of women. The probable pathological and physiological mechanisms of erectile dysfunction associated with various diseases are shown in table 2.

**Table 2: Subtypes of chronic dyspareunia in men**

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**Female genital arousal disorder and reduced lubrication**

Studies of symptomatic deficiency in genital vaso-congestion with progression of cardiovascular disease in women are much less common than those in men. One partly retrospective study showed that atheroma of the

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**Table 3: Diseases and drugs associated with erectile dysfunction**

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**Medical disorder**

<table>
<thead>
<tr>
<th>Pyropie’s disease</th>
<th>Type of pain</th>
<th>Findings on physical examination</th>
<th>Therapeutic options and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on erection and difficulty with penetration</td>
<td>Penile curvature due to the formation of a plaque of fibrous tissue</td>
<td>Spontaneous improvement is likely. Patients should be advised to continue coital activity. No non-invasive treatments have been shown to help. Surgical correction should not be attempted for at least 12 months after onset or until symptoms have been stable for at least 3 and preferably 6 months.</td>
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**Phimosis:** usually idiopathic, but can be associated with candidosis

| Penile pain, itching, or both; preputial ballooning during voiding; voiding pain; slow urinary stream; and urinary frequency | Inability to exteriorise the glans penis | A normal state until age 5. Based on CE, later phimosis might be prevented by genital hygiene and gentle retraction of the foreskin without causing pain; moderately potent topical steroids might be beneficial. Otherwise surgery, such as preputial plasty (in which no skin is removed) or circumcision, might be necessary. |

**Priapism**: sickle cell disease, thalassemia major, leukaemia, erector genitores, antidepressant drugs, antihypertensive drugs, recreational drugs, and malignancy

| A persistent (and after a variable length of time, painful) unwanted erection that is not associated with sexual desire or sexual stimulation. | 1. Low-flow, ischaemic or anoxic priapism. 2. High-flow well oxygenated priapism, in which pain is less of a feature. 3. Recurrent or stuttering priapism, usually high-flow but can become low-flow and anoxic. Frequently associated with sickle-cell disease. | 1. In early stages, advise micturation, application of ice pack, cold showers; give analgesics or terbutaline for a pharmacologically prolonged erection. A low-flow ischaemic priapism requires urgent treatment to prevent muscle necrosis; aspiration of cavernous blood can confirm the diagnosis of a low-flow ischaemic priapism, relieve pain, and reduce pressure. If this treatment does not produce sufficient results after 10 minutes, an α adrenoreceptor agonist should be injected. This should be repeated, and detumescence maintained, for 1 hour, followed by shunt-surgery. 90% of men with a priapism lasting 24 hours do not regain the ability to have intercourse unless a penile prothesis is implanted. 2. This disorder can resolve spontaneously; if not, selective embolisation with autologous blood clot or surgical ligation of a fistula is usually successful. | 1. In early stages, advise micturation, application of ice pack, cold showers; give analgesics or terbutaline for a pharmacologically prolonged erection. A low-flow ischaemic priapism requires urgent treatment to prevent muscle necrosis; aspiration of cavernous blood can confirm the diagnosis of a low-flow ischaemic priapism, relieve pain, and reduce pressure. If this treatment does not produce sufficient results after 10 minutes, an α adrenoreceptor agonist should be injected. This should be repeated, and detumescence maintained, for 1 hour, followed by shunt-surgery. 90% of men with a priapism lasting 24 hours do not regain the ability to have intercourse unless a penile prothesis is implanted. 2. This disorder can resolve spontaneously; if not, selective embolisation with autologous blood clot or surgical ligation of a fistula is usually successful. |

**Dermatologic diseases**

| Pain on touch and penetration. | Visible symptoms, dysfunctional foreskin, or both. | Exclude sexually transmitted disease. Treat underlying disorder (see table 5). Based on CE, counsel couples about non-penetrative and safe sex. Also, give psychosexual support for sexual difficulties from limited skin contact, visible symptoms, disrupted self-image, inability to meet a partner, shame, or lack of confidence. |

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**Table 3: Subtypes of chronic dyspareunia in men**

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**Footnotes:**


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**Series**
hypogastric arteries, pudendal arteries, or both was associated with reduced lubrication and perceived negative effects on sexual function, which became more severe after surgical vascular intervention, despite improved general health. Reduced lubrication is the only sexual dysfunction consistently seen more commonly in women with diabetes than in those without. 21,22,30,38 Premenopausal women with mild hypertension, irrespective of treatment, have more lubrication difficulties and fewer orgasms than age-matched controls.30 Vaginal congestion is reduced in women who receive haemodialysis or peritoneal dialysis, and this effect persists after renal transplantation, despite improved subjective arousal.30 Oestrogen-deficiency is traditionally associated with reduced lubrication in response to sexual stimuli. Estrone, produced mostly from adrenal androstenedione, is the predominant oestrogen in postmenopausal women. Genes activated by oestrogen and oestrogen-agonists include those that have a role in vascular response, such as nitric oxide synthase, prostacyclin synthase, endothelin-1, fibrinogen, plasminogen activator inhibitor, and tissue plasminogen activator. Moreover, beneficial effects on lipids (which are themselves adversely affected by menopause) add to oestrogen’s potential vascular benefit. Although signs of vaginal atrophy from low oestrogen levels correlate inversely with basal measures of vaginal congestion, the increase in the proportion of congestion in response to erotic stimuli is similar in oestrogen depleted and replete states.39 Similarly, changes in the vaginal wall and clitoral volume with sexual stimulation are comparable before and after menopause.40 Lower postmenopausal oestrogen levels do not necessarily preclude adequate lubrication if stimulation is sufficient: other factors, such as smoking41 and previous vaginal deliveries,42 might have a role. Nonetheless, sexually symptomatic vaginal atrophy might affect about 50% of postmenopausal women.43 Also, low oestrogen increases the pH of the vaginal lumen, which increases susceptibility to infection, and in turn undermines women’s sexual self-confidence and contributes to dyspareunia. Vaginal-ectocervical cells have been shown to acidify the vaginal lumen by secretion of protons across the apical plasma membrane. This active proton secretion is thought to happen throughout life but to be up-regulated by oestrogen.44 Local oestrogen therapy is recommended for dyspareunia, recurrent urinary tract infection, and loss of sexual genital sensitivity.45

Pathophysiology of excessive genital congestion
Priapism is persistent erection of the corpora cavernosa despite absence of sexual stimulation and subjective sense of sexual arousal. Risk factors and management for this disorder are shown in table 3.155–177 So-called

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Associated disease</th>
<th>Associated drugs</th>
<th>Therapy and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature ejaculation.</td>
<td>Prostatitis, epididymitis, urethritis, or SCI</td>
<td>Withdrawal from opiates, ephedrine, or trifuoperazine.</td>
<td>Give SSRIs, especially paroxetine (5-HT2C stimulation),123 with cognitive-behavioural techniques including stop-start and pubococygeal muscle training based on CE.124</td>
</tr>
<tr>
<td>Delayed or absent</td>
<td>SCIs, especially if complete UMNL, MS, or very</td>
<td>SSRIs and antipsychotics.</td>
<td>Prescribe use of vibrator, with or without yohimbine, bupropion, buspirone, or cyproheptadine (based on CE). If fertility needed use viberostimulation or electroejaculation,125 with attention to autonomic dysreflexia for lesions above T6. Give sildenafil to reverse SSRI-induced delay.125</td>
</tr>
<tr>
<td>ejaculation and orgasm.</td>
<td>low testosterone.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orgasm present,</td>
<td>Very low testosterone; damage to pelvic sympathetic nerves from RPND or pelvic surgery; SCI, MS, or diabetes.</td>
<td></td>
<td>Testosterone replacement if not contraindicated. Vibrator with or without yohimbine, bupropion, buspirone, cyproheptadine (based on CE). If fertility needed: viberostimulation or electroejaculation,125 with attention to autonomic dysreflexia for lesions above T6. Give sildenafil to reverse SSRI-induced delay.125</td>
</tr>
<tr>
<td>ejaculation absent.</td>
<td>Diabetes; MS; TURP; bladder neck surgery; damage to pelvic sympathetic nerves from pelvic surgery; or RPND.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrograde ejaculation,</td>
<td>Prostatitis (acute or chronic); epididymitis; urethritis; LUTS; post-traumatic urethral strictures, genital tract stones.</td>
<td></td>
<td>Treat underlying disorder. Tamsulosin can be of benefit when underlying urological pathology is clearly identified,126 but not when absent.127</td>
</tr>
<tr>
<td>confirmed by sperm in urine or TRUS showing open bladder neck at rest.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful ejaculation.</td>
<td>Prostatitis, epididymitis, or SCI</td>
<td></td>
<td>Treat underlying disorder. Tamsulosin can be of benefit when underlying urological pathology is clearly identified,126 but not when absent.127</td>
</tr>
<tr>
<td>Low-volume ejaculation.</td>
<td>Low testosterone; urethral strictures;ejaculatory duct obstruction; or LUTS.</td>
<td>Tamsulosin or antiandrogens.</td>
<td>Treat underlying disorder. Could be caused by ageing.</td>
</tr>
<tr>
<td>Female orgasm</td>
<td>SCI (especially complete UMNL), or MS.</td>
<td>Antipsychotics, SSRIs, and antiandrogens.</td>
<td>From risperidone but not olanzapine in small open label study. Increase stimulation (eg, stronger vibrator based on CE). Bupropion effective in one of two RCTs for SSRI-induced delay124 Surgical intervention is the definitive therapy for incontinence; but it worsened sexual function in 71% of patients and improved sexual function in only 29%.62</td>
</tr>
<tr>
<td>delayed or absent.</td>
<td>Low testosterone states or LUTS; (especially urge incontinence).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female orgasm</td>
<td>SCI (especially complete UMNL), or MS.</td>
<td>Antipsychotics, SSRIs, and antiandrogens.</td>
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</tr>
<tr>
<td>Painful female orgasm.</td>
<td>Post menopause; IUD; pelvic inflammatory disease; endometriosis; pelvic floor dysfunction.</td>
<td></td>
<td>Postmenopausal oestrogen and progesterone (based on CE). Treat underlying disorder.</td>
</tr>
</tbody>
</table>

CE=clinical experience. IUD=intruterine device. LUTS=lower urinary tract symptoms. MS=multiple sclerosis. RCT=randomised controlled trial. RPND=retroperitoneal lymph node dissection. SCI=spinal cord injury. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. TRUS=transrectal ultrasound. TURP=transurethral prostatectomy. UMNL=upper motor neuron lesion.

Table 4: Diseases and drugs associated with dysfunction of orgasm and ejaculation.
women’s persistent genital arousal syndrome, a recently recognised disorder that is somewhat similar, is intrusive, unwanted, persistent genital congestion with preorgasmic feelings, which is only slightly relieved by orgasm. Neither medical susceptibility factors nor effective treatment are known.

**Orgasm dysfunction**

A full understanding of the physiology of orgasm in men and women remains unclear. Orgasm has been variously defined as a “psychic phenomenon, a sensation (cerebral, neuronal discharge) elicited by the accumulative effect on certain brain structures of appropriate stimuli originated in the peripheral erogenous zones” or the “acme of sexual pleasure of rhythmic contraction of perineal/reproductive organs, cardiovascular, and respiratory changes, release of sexual tension”. Increases in oxytocin with arousal have been inconsistently documented in human beings, and increases in prolactin after orgasm have not yet been shown to have functional implications. Consistent with the fact that men and women with complete spinal-cord injury can experience orgasm is the view that orgasm is primarily a cerebral event. The absence of rhythmic contraction of perineal muscles and absence of genital sensations in spinal-cord injury does not prevent the recognition of orgasm. Imaging studies in health and in spinal-cord injury suggest that, during orgasm, specific regions of the brain are activated over and beyond those activated during arousal, while others are deactivated. This leads to reduction of inhibitory serotonergic tone from the nucleus paragigantocellularis to the so-called orgasm centre in the lumbarosacral cord. Although genital sexual stimulation is the most common stimulus, sexual pain disorders are highly correlated. For recurrent cystitis give local OT, systemic antibiotics, or the whole introital rim. Hypertonic perineal and vulvar inflammation. Perineal and vulvar inflammation. Voiding dysfunction, recurrent bacterial cystitis, hypoactive sexual desire, and sexual pain disorders are highly correlated. For recurrent cystitis give local OT, antibiotic self-treatment or prevention, and postcoital micturition (based on CE). In case of prolapse, surgical treatment can be curative but can also have undesired effects on sexual functioning.

**Medical disorder** | **Type of dyspareunia** | **Findings on physical examination** | **Therapeutic options and general comments**
--- | --- | --- | ---
Vulvovaginal atrophy: associated with renal failure, chemotherapy-induced menopause, hypothalamic or pituitary disease, bilateral oophorectomy, or hyperprolactinaemia. | Intestinal pain and with penile-vaginal movement, Possible postcoital burning. Deeper dyspareunia when vaginal atrophy advanced. | Pallor, dryness, increased fragility and thinning of vulvovaginal epithelium, vaginal shortening, loss of rugae, narrowing, or urethral caruncle. | Local oestrogen therapy is highly recommended. Low-dose estradiol by vaginal ring or tablet can be equally effective, but serum levels remain postmenopausal. Tibolone improves this disorder beyond placebo. Frequent sexual arousal and (if necessary) non-penetrative activity could promote genital health. Give dopaminergic drugs such as bromocriptine, cabergoline, or both to reduce prolactin; with surgery or radiation as appropriate.

Chronic (abdominal) pain: Endometriosis, Chronic PID; IBS; Crohn’s disease; Ulcerative colitis; Ovarian tumour; Abdominal wall pain. | Deep dyspareunia. IBS also associated with introital pain from concomitantly VVS. | General tenderness to deep bimanual examination. | Sexual dysfunction is highly prevalent in such patients. Women report deep dyspareunia. Organic disorders should be treated accordingly but sexual dysfunction may still need to be specifically managed. Irrespective of the organic or functional nature of the pain, a history of possible negative sexual experiences should be elicited before any procedures or treatment.

Lower urinary tract symptoms (LUTS) with urinary incontinence. | Intestinal and deep dyspareunia or vulvar burning after sexual intercourse. |  | Preventive measures, such as transposition of the ovaries to prevent ovarian failure. Therapeutic options based on CE include couple counselling about non-penetrative sex, topical oestrogen, lubricants, vaginal inserts, and vaginal reconstruction.

Pelvic radiation. | Intestinal and deep dyspareunia. | Thinning and fragility of vaginal epithelium, loss of elasticity, stenosis, or foreshortening. | Oral agents recommended for recurrent symptomatic candidiasis.

Chronic vulvovaginal candidiasis associated with diabetes and HIV. | Intestinal dyspareunia and with penile-vaginal movement. |  | Vaginal muscle EMG biofeedback with pelvic floor physical therapy and CBT have been shown to have clinical benefit, but evidence is limited. Based on CE treatment with topical oestrogens, cromolyn, xylacaine, capsaicin, or botulinum toxin injections. Based on CE, and the not yet proven assumption that neuropsychiatric pain is at least in part responsible for the pain of VVS, use TCA or AEDs. For comorbid IC, DBPCTs have shown benefit of oral or intravesical pentosan polysulfate, intravesical dimethyl sulfoxide or resiniferatoxin (vallinoid). Based on CE, there may also be benefit from antihistamines, quercetin, intravesicalepirin, lidocaine, or a combination. Excision of the affected regions (vestibulectomy, vestibuloplasty, or perineoplasty) can reduce pain in the short term but long term sexual outcome less clear.

Vulvar vestibulitis syndrome (VVS) associated with IBS, fibromyalgia, intestinal cystitis (IC), and other pain syndromes. | Superficial vulvovaginal pain on (attempted) penetration, pain on non-penetrative vulvovaginal touching, postcoital burning, or burning from partner’s ejaculation fluid. | Variable erythema of the vestibule. Alloodynia typically located between 4 and 8 o’clock on the introitus, just exterior to the hymenal ring but can involve the skin around the openings of the Skene’s ducts on the whole introital rim. Hypertonic pelvic floor muscles. Pain with attempted digital or speculum entry. | Vaginal muscle EMG biofeedback with pelvic floor physical therapy and CBT have been shown to have clinical benefit, but evidence is limited. Based on CE treatment with topical oestrogens, cromolyn, xylacaine, capsaicin, or botulinum toxin injections. Based on CE, and the not yet proven assumption that neuropsychiatric pain is at least in part responsible for the pain of VVS, use TCA or AEDs. For comorbid IC, DBPCTs have shown benefit of oral or intravesical pentosan polysulfate, intravesical dimethyl sulfoxide or resiniferatoxin (vallinoid). Based on CE, there may also be benefit from antihistamines, quercetin, intravesicalepirin, lidocaine, or a combination. Excision of the affected regions (vestibulectomy, vestibuloplasty, or perineoplasty) can reduce pain in the short term but long term sexual outcome less clear.

Dysaesthetic vulvodynia. | Intestinal dyspareunia, and with penile-vaginal movement. | None. | Vulvar burning and pain that causes sexual and psychological distress accompanied by the complete absence of any physical abnormality on examination, in biopsies or culture. Based on CE, TCA or AEDs can be of partial benefit.

Genital mutation. | Intestinal pain and with penile-vaginal movement and deep dyspareunia. | Type I: all or part of the clitoris and its prepuce or skin excised. Type II: clitoris excised, labia minora partly or totally removed. Type III: all external genitilia excised, vaginal opening closed except for a match-tip-sized hole to allow urine and blood to escape. | Experienced by an estimated 130 million women, in particular from north Africa, the middle east, and southeast Asia. Based on CE, use a respectful approach and provide information about health consequences. Offer sexual counselling, psychotherapy, and support groups. Offer to repair the vulva, vagina, or both. Involve the partner, the family, or both in decisions. Clarify the legal and ethical responsibility of the physician, who must decline any request to restitch after childbirth. Offer specific management of sexual dysfunction as needed.
fantasy, sexual dreams, and physical stimulation of other areas (eg, the nipple) can trigger orgasms in men and women. Women with complete spinal-cord injury above the spinal-cord level T10 can have orgasms from vibrostimulation of the cervix, possibly mediated by way of vagal afferents.122

Table 4123–127 shows neurological disorders that delay or preclude orgasm in men and women.14 Damage to the pelvic autonomic plexuses (eg, from radical prostatectomy or radical hysterectomy) does not preclude orgasm. The necessary autonomic nerves probably travel with somatic fibres S2, S3, S4; there are branches from sympathetic ganglia to the union of S2, S3, S4 parasympathetic and somatic fibres proximal to the superior hypogastric plexus. Contrary to clinical impressions, weakening of the pelvic floor from vaginal deliveries is not correlated with sexual dysfunction.129 The most common drugs that impede orgasm are the selective serotonin reuptake inhibitors.

Ejaculatory dysfunction
Ejaculation consists of sympathetically mediated emission of seminal fluid into the posterior urethra and somatically mediated expulsion of the ejaculate. Animal studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates ejaculation by way of 5-HT₆ receptors and inhibits it by way of 5-HT₃ receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.219

Chronic dyspareunia
Prevalence figures for chronic dyspareunia vary from 6·5% to 40% in older women, and 14% to 34% in younger women.211,212–213 to 1% in men.113 Dyspareunia in women frequently arises in the context of chronic disease (table 5), and in men is usually related to Peyronie’s disease (table 3). Irrespective of the associated chronic disease, the initial pathophysiological mechanisms of women’s dyspareunia are often unclear, but central and peripheral sensitisation of the nervous system might be the overriding process. Pain is normally reported when impulses reach the brain via A δ fibre or C-fibre nociceptive afferents. In chronic pain the threshold of nociceptors is reduced by the release of chemical inflammatory mediators into the tissue, which causes peripheral sensitisation. Nociceptors can become sensitised to weak, non-noxious stimuli, which results in allodynia, and to noxious stimuli, which results in the exaggerated pain response of hyperalgesia. Allodynia and hyperalgesia can also be due to central sensitisation, in which signals entering the central nervous system via non-nociceptive A β touch–afferents are amplified abnormally, so that they evoke pain. The cause of the increased descending excitatory signals, decreased inhibitory signals, or both, which produce central sensitisation of dorsal horn cells, is unclear. We need to know whether psychological factors, such as the expectation of pain from a highly intimate behaviour (normally associated with pleasure and emotional release), have a role.

Vulvar vestibulitis syndrome is the most common subtype of chronic dyspareunia, and affects about 9% of women.219 Although reported predominantly in young, otherwise-healthy women, vulvar vestibulitis syndrome also affects older women, especially those diagnosed with other pain disorders such as fibromyalgia and irritable...
bowel syndrome. This disorder is characterised by burning pain localised at the entrance (vestibule) of the vagina from sexual and non-sexual contact. Both the primary form of vulvar vestibulitis syndrome (from the first intercourse attempt) and the secondary form are of uncertain aetiology. Genetic factors could act to reduce the production of interferon or mannose-binding lectin, which are of importance for innate resistance against microorganisms. Vulvar vestibulitis arises most commonly in the presence of specific alleles of the interleukin-1 receptor antagonist and melanocortin-1 receptor, which are associated with pale skin and increased risk of infections.

Most women with vulvar vestibulitis syndrome also have spontaneous dysaesthesiae in the form of vulval burning (vulvodynia), consistent with neuropathic pain. Vulvodynia can happen premenstrually, or intermittently or constantly throughout the monthly menstrual cycle. Increased numbers of intraepithelial nerve-endings, possibly as a consequence of mast-cell activity in repeated inflammation, could contribute to the hyperalgesia. Women with vulvar vestibulitis syndrome show generally increased sensitivity to pain stimuli. Augmentation of genital sensory processing, similar to that recorded in fibromyalgia, idiopathic back pain, irritable bowel syndrome, and neuropathic pain at non-genital sites, can be seen on functional MRI of the brain. Therefore, vulvar vestibulitis syndrome might include mechanisms that are genital-specific in addition to those that are generalised, and possibly centrally mediated.

A subgroup of patients with vulvar vestibulitis syndrome have a history of recurrent candidiasis. Candida can induce an immunological response that results in pathological changes in cutaneous T-lymphocyte cells and chronic inflammatory skin disease in genetically susceptible women. Compared with women with other skin disorders, women with vulvar vestibulitis syndrome were significantly more likely to react to Candida albicans (but not other standard allergens or vulval organisms) on patch testing.

Whether as a cause or a consequence, pelvic floor hypertonia is typically present in vulvar vestibulitis syndrome in common with irritable bowel syndrome, constipation, haemorrhoids, interstitial cystitis, and instances of chronic abdominal pain. The pelvic floor musculature is indirectly innervated by the limbic system and therefore, is highly reactive to emotional stimuli and states. Moreover, coitus entails an anatomical match or mismatch between penis and the degree to which the woman can relax. Penile diameter does appear to be relevant when the woman has vulvar vestibulitis syndrome.

Initiation of hormonal contraceptives that contain low-dose oestrogen before the age of 16 could predispose women to vulvar vestibulitis syndrome. A significantly lower pain threshold, especially in the posterior vestibulum, has also been associated with the use of hormonal contraceptives in women without vulvar vestibulitis syndrome. Despite earlier contradictory data, recent studies confirm that women with vulvar vestibulitis syndrome have high levels of psychological distress, depression, pain catastrophisation (irrational escalation of negative thoughts on pain), anxiety-disorders, perfectionism, somatisation (physical symptoms from psychological distress), and harm avoidance. These women also report hyper-vigilance for coital pain and exhibit a selective attention bias towards pain stimuli. Mechanisms of the mind can initiate processes such as neurogenic inflammation. However, women with vulvar vestibulitis syndrome are more sensitive than other women to noxious stimuli, irrespective of their personality traits.

The treatments for dyspareunia outlined in table 5 are not evidence-based; they include chronic-pain medications along with sexual and psychological counselling. Non-penetrative sex is advocated. Partial or complete vestibulectomy can bring short-term relief of dyspareunia, but conservative treatment can be equally efficient for management of pain, and fear of pain, during intercourse. Research has shown that patients’ acceptance of the rationale for their treatment correlates with better outcome and reduction of pain.

Although the aetiology of dyspareunia must be investigated with careful clinical examination, this might be impossible initially in some women with histories of chronic introital dyspareunia who are unable to tolerate any entry by a penis, dildo, or tampon, and show muscle tightening or fear that is characteristic of vaginismus. In such patients, examination is deferred until after treatment, such as education about vaginismus, cognitive behavioural therapy, and sex therapy, allows a detailed examination and the subsequent use of graded vaginal inserts. Physicians treating women with vaginismus commonly note exaggerated disgust and aversion to contact with sexual fluids, religious orthodoxy, negative messages about sex from childhood, a history of poorly executed attempts at pelvic examination, and unassertiveness of a male partner. As with vulvar vestibulitis syndrome, outcome for treatment of vaginismus is not scientifically validated. Although many clinicians define vaginal penetration as the goal of treatment, future outcome measures should be broadened to include attainment of sexual pleasure.

For the treatment of dyspareunia in general, a multidimensional, multidisciplinary approach is recommended, with attention to the patient’s experience of pain; their emotional and psychological profile; any past genital mutilation or sexual abuse; the genital mucous membrane; the pelvic floor; and the sexual relationship.

Integrating medical and psychosocial effects of disease on sexual function
In middle-aged and elderly men and women, attitudes about sexual intercourse, and about the disease in
Medical factors resulting from disease, treatment, or both
- Fatigue, pain, incontinence, or changed anatomy of sexual organs
- Reduced mobility which limits ability to caress, stimulate self or partner, or engage in intercourse
- Changed physical sensations, such as itching, irritation, insensitivity, or hypersensitivity
- Interruption of sexual response, infertility, dyspareunia, or painful ejaculation or orgasm
- Angina or dyspnoea from sexual stimulation

Psychological response to illness or sexual dysfunction
- Fear that sex could be dangerous, and provoke myocardial infarction or cerebral vascular accident
- Fear of infection or conviction that illness was caused by sexual activity (eg, cancer as punishment)
- Preoccupation with illness or loss of control and independence
- Disrupted sexual self-image or feeling failure as a sexual partner or potential parent
- Anxiety, depression, anger, shame, guilt, stress, or emotional liability
- Avoidance behaviour, fearing pain or rejection due to disfigurement or stoma
- Repeatedly remembering traumatic medical procedures to sexual parts

Personal psychological factors
- Limited coping mechanisms or negative attitude
- History of limited or unrewarding sexual experiences
- Past abuse (sexual, physical, or emotional)

Psychological response to illness or sexual dysfunction
- Interruption of sexual response, infertility, dyspareunia, or painful ejaculation or orgasm
- Changed physical sensations, such as itching, irritation, insensitivity, or hypersensitivity
- Reduced mobility which limits ability to caress, stimulate self or partner, or engage in intercourse
- Fatigue, pain, incontinence, or changed anatomy of sexual organs

question, can have a more significant effect on sexual function than do biomedical factors. Also, especially in women, feelings of intimacy are often more important than feelings of sexual arousal. Whereas sexual function is affected by physical sensations, mobility, and physiological changes in the genital region, the appreciation of intimacy is far less dependent on physical capacities. Sexual dissatisfaction in chronic disease is therefore highly variable, and is strongly modulated by personal, societal, and relationship factors, and by past experiences, all of which need to be taken into account when sexual dysfunction is addressed (panel).

Future directions
Both an increased understanding of sexual physiology and a wider acceptance that sexuality is often an important part of life might encourage physicians to routinely consider risk factors for sexual dysfunctions, to assess and manage those dysfunctions, and to avoid iatrogenesis. Improved assessment, which includes validated questionnaires revised to take account of contemporary views of sexual response, could increase our understanding of the prevalence of sexual dysfunction in different patient cohorts. Inclusion of men and women who are no longer sexually active into relevant studies is a desirable goal.

We need to investigate whether pharmacological or non-pharmacological treatments of vascular risk factors can improve deficient genital congestion and whether antagonists of the renin angiotensin system are more able to decrease oxidative stress injury than other treatments. Erectile dysfunction might be an appropriate outcome measure for clinical trials of lipid-lowering drugs; one prospective study has suggested that an improvement to risk factors for coronary heart disease in midlife will lessen the frequency of both erectile dysfunction and coronary artery disease.

Acknowledgments
We thank Dr Peter Rees for his helpful review of the manuscript and Maureen Piper for her excellent secretarial support.

Conflict of interest statement
R Basson was a temporary consultant to Pfizer (about the relation between female sexual dysfunction and a molecule under investigation) and on one occasion to Solvay. Her clinical practice occasionally necessitates provision of medicolegal reports without prejudice. W Weijmar Schultz is participating in an international study to assess the effects of Lival on sexual functioning over and above its ability to relieve climacteric symptoms in postmenopausal women with sexual dysfunction. This study is financed by Organon. He has no personal financial relations with this company.

Contributors
R Basson wrote the first ten sections and the future outlook. She also edited other sections. W Weijmar Shultz wrote the three sections on dyspareunia in men and women and on the integration of medical and psychosocial effects of disease on sexual function. Both authors have read and approved the final version.

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